

MILD COGNITIVE IMPAIRMENT:
IMPROVED IDENTIFICATION AND A NOVEL
COGNITIVE INTERVENTION

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Abstract

The prevention and treatment of cognitive impairment in the elderly has assumed increasing importance given the ageing population. Mild Cognitive Impairment (MCI) is considered as a transitional state between healthy ageing and dementia. The primary aim of the current study was to develop a cognitive intervention for MCI that encourages participation in a variety of complex and novel cognitive activities, and to examine its efficacy. Furthermore, these cognitive activities were developed to influence multiple brain networks, particularly the default mode network (DMN). A secondary aim was to assess the diagnostic utility of a number of screening measures in discriminating MCI.

In the Cognitive Screening Study, 609 individuals (age range 65-97 years old) were evaluated using brief cognitive tests, including the Montreal Cognitive Assessment (MoCA), Rey Complex Figure Test (RCFT; copy and 3-min recall), and Trail Making Test-Part A (TMT-A). After the initial evaluation, 222 were excluded, the remaining were classified as Probable MCI ($n = 75$), Possible MCI ($n = 72$) and Probable Healthy Control (HC; $n = 240$). A portion of these individuals were followed-up with detailed cognitive assessment, and their performance on the detailed assessment determined which cognitive group they were assigned to. As a result, 17 individuals were classified as Confirmed MCI, 91 as Possible MCI, and 226 as Probable HC. The diagnostic utility of

each individual screening measure was examined using the standard receiver operating characteristic curve (ROC). Multivariate logistic regression analysis was conducted to investigate whether combinations of the screening instruments improved the detection of MCI. Simultaneous discriminations among the three cognitive classes were examined using three-dimensional ROC. The results revealed that both MoCA and RCFT (copy and 3-min recall) demonstrated good discrimination of MCI, however, the combination of the two tests showed even better discriminatory power.

Thirteen MCI participants were included in the Cognitive Enrichment Study, these individuals were randomly allocated to either the intervention ($n = 6$) or waitlist group ($n = 7$). Those in the intervention group received the 4-month-long Cognitive Enrichment Programme. Although the neuropsychological results were generally non-significant, we found a significant pre-post-effect on a measure of long-term memory retrieval. Furthermore, this study also used functional magnetic resonance imaging (fMRI) to examine the effect of enrichment on the DMN in MCI. DMN activity and connectivity were recorded pre- and post-enrichment. An increase in resting-state DMN connectivity was found in intervention participants, while the waitlist group showed a reduced connectivity. The changes in DMN connectivity were associated with an improvement on tests of executive function. However, there were no enrichment-related changes in DMN activation and deactivation. In conclusion, these results suggest some beneficial effects of cognitive enrichment on cognitive abilities, as well as DMN connectivity. Results from the current study, however, should be interpreted with caution because of the small

sample size. Further larger trials are needed to confirm the preliminary findings of this study.

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List of Abbreviations

ACE-R	Addenbrooke's Cognitive Examination-Revised
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
aMCI	Amnesic Mild Cognitive Impairment
AMI	Autobiography Memory Interview
ANCOVA	Analysis of Covariance
APOE	Apolipoprotein E
AUC	Area Under the Curve
BDNF	Brain Derived Neurotrophic Factor
BOLD	Blood-Oxygen-Level Dependent
BVMT-R	Brief Visuospatial Memory Test-Revised
CANTAB	Cambridge Automated Neuropsychological Test Battery
CDR	Clinical Dementia Rating
CI	Confidence Interval
CVLT-II SF	California Verbal Learning Test-Second Edition Short Form
DMN	Default Mode Network
DRS-2	Dementia Rating Scale-2
EE	Environmental Enrichment
EPI	Echo Planar Imaging
FLAIR	Fluid-Attenuated Inversion Recovery
fMRI	Functional Magnetic Resonance Imaging
GIFT	Group ICA toolbox
GOF	Goodness of Fit
HC	Healthy Control
ICA	Independent Component Analysis
JLO	Judgement of Line Orientation
M	Mean
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination

MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
naMCI	Non-Amnestic Mild Cognitive Impairment
NPV	Negative Predictive Value
NZBRI	New Zealand Brain Research Institute
PET	Positron Emission Tomography
PiB	Pittsburgh Compound B
PPV	Positive Predictive Value
RCFT	Rey Complex Figure Test
RCT	Randomised Control Trial
RI-48	Rappel Indice 48 Items
ROC	Receiver Operating Characteristic
RS-fMRI	Resting-State Functional Magnetic Resonance Imaging
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SPGR	Spoiled Gradient Recalled Echo
TBI	Traumatic Brain Injury
TMT	Trail Making Test
vMCI	Vascular Mild Cognitive Impairment
VUS	Volume Under the ROC Surface

CHAPTER 1 - General Introduction

1.1 Cognitive Decline in Older People

The lifespan of the general population is increasing as a result of advances in medical science and the availability of better healthcare services. The proportion of elderly persons is therefore also rising. New Zealand, like many other countries, has an ageing population. The proportion of people aged 65 and over has doubled since 1980, and is likely to double again by 2036 (StatisticsNewZealand, 2014). This rapidly ageing demographic, however, has a major downside, namely age-associated cognitive decline and dementia. Alzheimer's disease (AD), the most common cause of dementia, is a major source of caregiver burden, disability, institutionalisation and mortality in old age (Goedert & Spillantini, 2006; Jorm & Jolley, 1998). Moreover, it has emerged as a critical public health emergency in many countries, as the number of older adults living with the disease is predicted to increase from the current 44 million to more than 132 million by 2050 globally (Alzheimer'sAssociation, 2014).

Another concern is that AD is probably the most expensive condition for our current health system (Alzheimer'sAssociation, 2014). Indeed, it is uncertain whether it will be possible to care for and treat all persons with dementia in the coming century (Lovestone, 2002). The societal need and fiscal costs have driven significant research

toward developing successful remedies for AD. Unfortunately, the progressive course of the disorder has yet to be significantly impacted by any of the developed therapeutic strategies to date.

1.2 The Need for Early Identification

AD is an insidious disorder that progressively worsens brain structure and function (Almkvist & Winblad, 1999; Braak & Braak, 1991). By the time AD is typically diagnosed, substantial neuronal loss and neuropathological changes have damaged numerous brain regions. Although it may be possible to reverse some aspects of this damage, it would be ideal to initiate intervention at a time when, or even before, AD is mildly symptomatic, and ideally prior to dementia. Thus, the detection of an early stage of partial symptomatology may then offer an opportunity for early intervention. Mild cognitive impairment (MCI) may represent this incipient stage. Individuals with MCI usually show cognitive deficits that are more severe than expected, based on age and educational background, and which do not as yet cause significant impairment in their everyday activities. Confirming the view that MCI represents a transition between normal ageing and dementia, these individuals are at increased risk for dementia. The annual rate of progression from MCI to AD is approximately 14%, which is markedly greater than the expected 1% to 2% annual incidence of AD (Petersen, 2004; Petersen et al., 1999).

Given this clinical significance, it is essential to differentiate MCI from normal cognition and AD. Cognitive screening provides an indication of the likely presence of clinically meaningful cognitive impairment and is usually the first step in the identification of MCI, prior to more elaborate assessments. Cognitive screening tests that are commonly used in clinical and research setting have been developed for the diagnosis of dementia and may not show adequate discrimination of MCI individuals. The Montreal Cognitive Assessment (MoCA) is a brief cognitive test specifically developed to screen for mild cognitive deficits and has been regarded as a suitable screen for people with suspected MCI (Lam et al., 2013; Nasreddine et al., 2005). While studies have demonstrated the MoCA as a sensitive measure for the detection of MCI, others have reported that MoCA is associated with a relatively poor specificity (Larner, 2012; T. Smith, Gildeh, & Holmes, 2007). The diagnostic accuracy of the MoCA can be improved with other supportive diagnostic techniques, such as the measurement of AD-related biomarkers in cerebrospinal fluid and/or structural and functional neuroimaging (Hoglund et al., 2015; Toledo et al., 2014; Willette, Calhoun, Egan, Kapogiannis, & Alzheimers Disease Neuroimaging, 2014). However, these techniques are often restricted to specialised settings and are not appropriate for large-scale screening of cognitive impairment. An alternative solution is the use of two or three brief cognitive tests in addition to the MoCA to improve the discriminatory power of the screening process. The rationale for this strategy is that different tests may provide supplementary information about the cognitive functioning of a given patient, increasing the probability of identifying those with mild deficits.

1.3 Treatment Options for MCI

There are currently no specific treatments for MCI, and both pharmacological agents and non-pharmacological intervention programmes have been examined as potential treatment options. The use of pharmacological treatment in persons with MCI has been a controversial topic. A recent systematic review demonstrated that the use of cholinesterase inhibitors (approved for AD treatment) have largely been unsuccessful in delaying disease progression or conversion to dementia in MCI patients (Karakaya, Fusser, Schroder, & Pantel, 2013). Additionally, factors such as cost and both immediate side effects such as gastrointestinal symptoms and vivid dreaming and longer term side effects such as bradycardia or syncope have also generated concerns with the use of cholinesterase inhibitors in MCI.

As there is currently no clear evidence of any benefits of pharmacological treatment, non-pharmacological interventions especially cognitive intervention, have attracted a lot of attention as a potential therapeutic approach for the MCI population. Persons with MCI are ideal targets for cognitive intervention, as these individuals are usually aware of, and often worried about, their cognitive changes, which is likely to increase their motivation to engage in treatment (La Rue, 2011). Perhaps more importantly, MCI individuals retain a large range of cognitive capacities. Previous research has demonstrated limited efficacy of cognitive intervention in AD patients (Sitzer, Twamley, & Jeste, 2006), possibly as a result of substantial neuronal loss and reduced brain plasticity. Brain plasticity is an important aspect in cognitive intervention

because it describes the brain's ability to change structurally and functionally in response to changes in the external environment and/or its integrity (Lovden, Backman, Lindenberger, Schaefer, & Schmiedek, 2010; Simos et al., 2000). Brain plasticity is still evident in MCI individuals, as measured by their abilities to learn new information and adapt their behaviour (Akhtar, Moulin, & Bowie, 2006; Schreiber & Schneider, 2007), making them ideal candidates for cognitive intervention.

Several lines of evidence from both animal and human studies have provided support for the hypothesis that participation in cognitive activities in humans, as well as environmental enrichment in animals, can lead to increased compensatory pathways in the brain and resilience to brain injury (Nithianantharajah & Hannan, 2006; Valenzuela, 2008; Verghese et al., 2003; Will, Galani, Kelche, & Rosenzweig, 2004). Furthermore, it is now clear that cognitive functions reflect the operation of complex and widely distributed brain networks over and above the influence of individual brain regions (Andrews-Hanna et al., 2007; Bressler, 1995; Bressler & Menon, 2010). In addition, recent evidence suggests that ageing-related cognitive decline is a result of alternations in functionally connected brain regions (Greicius, Srivastava, Reiss, & Menon, 2004; Mevel, Chetelat, Eustache, & Desgranges, 2011). Using functional magnetic resonance imaging (fMRI), multiple large-scale functional brain networks have been identified and described. Among them, the default mode network (DMN) has received most attention, because it contains brain areas associated with multiple higher-order functions and undergoes critical changes upon ageing as well as in neurodegenerative diseases,

particularly AD (Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Greicius et al., 2004; Gusnard, Raichle, & Raichle, 2001; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005). Regions of the DMN have consistently been found to show high levels of amyloid deposition even early in the course of AD (Leech & Sharp, 2014; Sheline et al., 2010). Thus, intervention programmes that engage a variety of cognitive processes, in the form of cognitive enrichment, would stimulate many large-scale brain networks and perhaps maximise efficacy than cognitive training programmes that focused primarily on memory function alone.

1.4 Aims of the Current Study

The main aim of the current study was to develop a cognitive intervention that encourages participation in a variety of novel cognitive activities for individuals with MCI (Chapter 5-7). A noticeable difference between the current study and former studies would be that the Cognitive Enrichment Programme was designed to influence multiple large-scale networks, but include a focus on the DMN, given its importance in the pathological processes in AD. Additionally, we sought to investigate the feasibility and efficacy of the Cognitive Enrichment Programme in MCI, and examine whether the beneficial effects relate to functional changes in the DMN. A secondary aim was to provide recommendations on the screening of MCI through the use of brief neuropsychological instruments (Chapter 3).

CHAPTER 2 - Mild Cognitive Impairment

2.1 Introduction

It is probable that there are indicators of future dementia occurring up to several years before the onset of the full dementia syndrome. Neurochemical and neuroimaging evidence suggests that neuropathological changes associated with dementia, and Alzheimer's disease (AD) in particular, may begin even decades before the onset of symptoms (Bookheimer et al., 2000; Braak & Braak, 1998). The growing emphasis on the importance of early identification of and interventions in dementia has led to attempts to define a distinct group of elderly with cognitive problems that exceed what is expected for their age, and educational and occupational attainment, but are not severe enough to cause everyday functional impairments to warrant a dementia diagnosis. This group of people are commonly referred to as mild cognitively impaired (MCI). The objectives of this chapter are to review relevant historical research on MCI, discuss how MCI is identified, and describe the effects of differing diagnostic criteria on its prevalence and rate of dementia conversion.

2.2 Historical Background

Over the last 50 years, several terms have emerged to describe and conceptualise the spectrum of conditions between normal ageing and pathological cognitive decline. These

terms include benign senescent forgetfulness (Kral, 1962), age-associated memory impairment (Crook et al., 1986), and late-life forgetfulness (Blackford & La Rue, 1989). These early constructs implied that such changes are part of ‘normal ageing’, and that many of these individuals are exhibiting normal age-related changes and are not expected to undergo significant further decline or harbour neuropathological changes. These terms are now recognised as inadequate. By the early 1980s it was clear that many individuals in this group are exhibiting prodromal symptoms of dementia and would progress to frank dementia eventually. It was in this historical context that the term MCI became widely accepted in the ageing and dementia literature (Flicker, Ferris, & Reisberg, 1991). During the 1990s and early 2000s, MCI increasingly gained acceptance as a pathological entity (i.e., not a manifestation of normal aging; Petersen, Doody, et al., 2001; Winblad et al., 2004). More recent work reflects variability in the use of the concept and recognises that a population of these cases may not develop dementia (Koepsell & Monsell, 2012; Mitchell & Shiri-Feshki, 2009; Prestia et al., 2013).

2.3 Diagnostic Definition and Clinical Subtypes

The diagnostic term MCI refers to cognitive impairment beyond that expected for age and education, but does not meet criteria for dementia (Petersen, 2004; Petersen, Doody, et al., 2001). Diagnostic criteria for MCI have undergone periodic revision since the original criteria published by Petersen et al. (1999). The original criteria conceptualised MCI as an amnesic condition. However, as the literature on MCI expanded, there have been

some observations that some individuals with MCI show a decline in memory only, while others show selective decline in other cognitive domains, such as executive function or visuospatial ability. In other MCI cases, mild decline is evident across multiple cognitive domains. Criteria for MCI have thus broadened to include both non-amnestic presentations and impairments in multiple cognitive domains. Although many researchers have suggested and used a variety of criteria for defining MCI, the general concepts in diagnosing MCI are (Petersen, 2004; Winblad et al., 2004):

- subjective cognitive complaints, or by a close informant;
- objective evidence of cognitive deficits lower than expected for age and educational background;
- preserved basic activities of daily living, and complex instrumental activities are either intact or mildly impaired;
- and do not meet criteria for a diagnosis of dementia.

With the advent of the revised criteria, clinical subgroups were also proposed to recognise that MCI is a heterogeneous diagnostic entity. An assumption has been that each subtype may be associated with different etiology, clinical presentation and prognosis. The most commonly used classification scheme is that recommended by Petersen et al. (2004). Four subtypes have been described and distinctions have been drawn between subtypes of MCI based on cognitive dysfunction:

- amnestic MCI single domain, where memory alone is affected;

- amnestic MCI multiple domain, where memory and at least one other area of cognition are affected;
- non-amnestic MCI single domain, where one cognitive domain other than memory is affected; and
- non-amnestic MCI multiple domain, where multiple domains of cognitive processes other than memory are affected.

In addition, Petersen and colleagues (2005) provided a flowchart illustrating a two-step process on how to differentiate between the subtypes (Figure 2-1). First, two primary subtypes were delineated, based on whether a predominant memory deficit was present (amnestic MCI) or absent (non-amnestic MCI). Second, it acknowledged the possibility that more than one cognitive domain may be impaired with each of the two primary subtypes (e.g., single or multiple domain impaired). Even though this classification is drawn from the neuropsychological tests administered for evaluating objective cognitive impairments, each subtype is presumed to reflect different etiologies and outcomes.

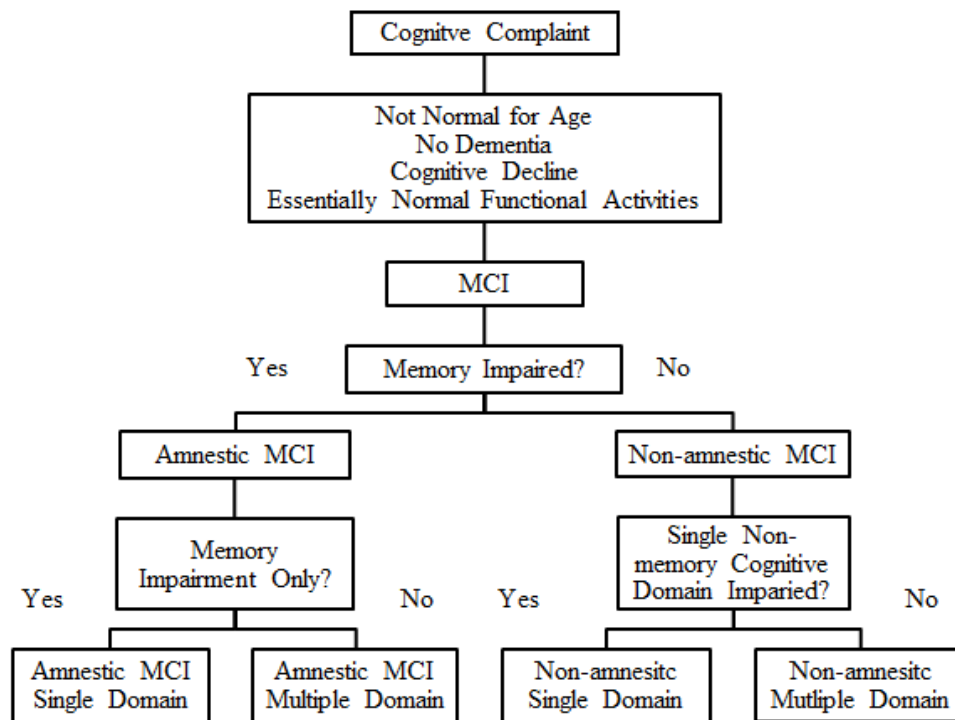


Figure 2-1. Flowchart for MCI diagnosis and subtyping.

Amnesic MCI (aMCI) has received the most attention among researchers, because it has been considered to be the most common form of MCI, and the most likely subtype to progress to AD (Petersen & Morris, 2005). Non-amnesic (naMCI) types were suggested as more likely to become dementia types such as Dementia with Lewy Bodies, Frontotemporal dementia or have a predominately vascular etiology (Petersen & Morris, 2005). Yaffe, Petersen, Lindquist, Kramer, and Miller (2006) examined the longitudinal trajectory of 327 MCI individuals after a 3.1 year follow-up. It was reported that among the participants who progressed to AD, 76% has a prior classification of aMCI and all participants who progressed to frontotemporal dementia had been previously classified as

naMCI. In a more recent longitudinal study, where the MCI participants were followed up for a longer period of time (7.5 years), the authors confirmed that the proportion of incident AD in aMCI individuals was significantly higher than in subjects with naMCI (Jungwirth, Zehetmayer, Hinterberger, Tragl, & Fischer, 2012). Furthermore, neuroimaging studies have shown that aMCI is associated with greater hippocampal and medial temporal atrophy than naMCI, and these biomarkers are assumed to be especially sensitive to AD pathology (Clerx et al., 2013; Duara et al., 2008). Studies of brain metabolism showed greater medial temporal hypometabolism in aMCI than naMCI (Clerici et al., 2009; Mosconi et al., 2008). Positron emission tomography (PET) studies using Pittsburgh Compound B (PiB), an amyloid probe, found significantly higher percentages of aMCI individuals were PiB-positive than individuals with naMCI (Pike et al., 2007; Wolk et al., 2009). Thus, AD-related neurodegenerative process has been suggested as the main etiology of individuals with aMCI. However, memory impairment could also evolve as a result of other conditions such as ischemia, cardiovascular and cerebrovascular diseases. Vascular risk factors are common among MCI, and the concept of vascular cognitive impairment (vMCI) has been introduced to emphasise the high prevalence of cognitive impairment when there is vascular damage to the brain, such as stroke or small vessel disease (Davis & Rockwood, 2004; Roman & Royall, 2004; Roman et al., 2004). However, many of these individuals show the same pattern of cognitive decline as aMCI (Loewenstein et al., 2006), and is likely that their cognitive deficits are often caused by mixture of AD pathology and cerebrovascular disease (Davis & Rockwood, 2004).

2.4 Epidemiology

The incidence of MCI and its subtypes ranges from 1% to 6% per year with a prevalence from 3% to 22% in the population older than 65 years (Bennett et al., 2002; Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001; DeCarli, 2003; J. E. Graham et al., 1997; Lopez et al., 2003; Petersen et al., 1999). The prevalence of MCI increases with age, similar to prevalence trends in AD shown in other studies (Lopez et al., 2003).

Individuals with MCI have a 4 to 10 times higher risk of developing dementia in comparison to cognitively normal elderly persons (Petersen, Stevens, et al., 2001).

Depending on the study, the overall annual conversion rate from MCI to dementia is between 10% to 15% per year (Bruscoli & Lovestone, 2004). So clearly not everyone with MCI goes on to develop dementia; some MCI individuals remain stable and other cases revert to a normal cognitive function (Bruscoli & Lovestone, 2004; Perri, Carlesimo, Serra, & Caltagirone, 2009). Concerns have been expressed over the ‘reverted’ MCI cases, which have led some to argue that MCI is an unstable diagnostic category (Larrieu et al., 2002; Ritchie, Artero, & Touchon, 2001). In contrast, a recent longitudinal study demonstrated that the ‘reverted’ MCI are still at greater risk for progression to dementia compared with persons who never were considered to have MCI. Roberts et al. (2014) identified 534 MCI at baseline, these individuals were subsequently examined every 15 months. They found that almost 40% of people with MCI reverted to cognitively normal during follow-up examinations. However, 65% of the ‘reverts’ developed dementia over a 5-year follow-up, which was 6 times the percentage of

cognitive normal subjects. This finding suggests that although MCI show fluctuations in cognition, the diagnosis of MCI at any time carries important prognostic implications.

2.5 Neuropsychological Evaluation

The diagnosis of MCI and its subtypes is mainly based on an individual's performance on standardised neuropsychological tests. Complaints such as subtle forgetfulness, problems in remembering names and common words, misplacing objects, and a lack of attention are very common among elderly people and may not necessarily be a sign of cognitive disorders (Lenehan, Klekociuk, & Summers, 2012; Mendes et al., 2008). Hence standardised neuropsychological assessment is considered to be optimal for objectively assessing the degree of cognitive impairment for an individual. However, specific neuropsychological measures included in the diagnosis varied widely from one study to the other. Many of the earlier studies have taken an amnesic-centred approach in the assessment of MCI. In these studies, memory functions are usually assessed by tests of episodic memory function, but non-memory functions are often neglected or inadequately assessed with measures of global cognitive function, which typically do not provide detailed information regarding functional abilities in any cognitive domains (Alexopoulos, Grimmer, Pernecky, Domes, & Kurz, 2006; Brodaty et al., 2013; Gavett et al., 2009; Jungwirth et al., 2012; Lonie, Herrmann, Donaghey, & Ebmeier, 2008).

Researchers taking a broader view of neuropsychological assessment have argued against the amnesic-centred approach, in saying that, such approach is likely to miss a sizeable proportion of MCI cases and contribute to the inaccurate identification of MCI subtypes (Alladi, Arnold, Mitchell, Nestor, & Hodges, 2006; Busse, Hensel, Guhne, Angermeyer, & Riedel-Heller, 2006). Obviously, these consequences are of significant concern, given findings that individuals with MCI are at increased risk for AD, and MCI subtypes differ in diagnostic outcomes and likelihood of progression to AD. The National Institute on Ageing have recommended for MCI studies to include a comprehensive assessment of memory and non-memory functions (Albert et al., 2011; Klekociuk, Summers, Vickers, & Summers, 2014; Mitchell, Arnold, Dawson, Nestor, & Hodges, 2009; Summers & Saunders, 2012). A detailed assessment of non-memory functions would ideally include measures of executive function, visuospatial function, attention and processing speed, and language abilities (Ghosh, Libon, & Lippa, 2013; Summers & Saunders, 2012). In addition, the diagnosis of MCI necessitates an abnormal change from baseline cognitive ability. Thus, estimation of premorbid baseline is important to gauge the significance of obtained test results. Table 2-1 provides an overview of the types of tests, grouped by cognitive domains, that may be used in the neuropsychological assessment to identify MCI. It is important to note that cognitive domains are not discrete entities. Even though a test may be designed to focus on one aspect of cognition, more often than not, test performance is influenced by multiple cognitive domains.

Table 2-1

Neuropsychological Tests, Grouped by Cognitive Domains, Commonly Used in the Assessment of MCI

Assessment of Baseline Intelligence
<ul style="list-style-type: none">• National Adult Reading Test• Wechsler Test of Adult Reading• Advanced Clinical Solutions – Test of Premorbid IQ
Measures of Global Cognitive Function
<ul style="list-style-type: none">• Mini-Mental Status Exam• Montreal Cognitive Assessment• Dementia Rating Scale-2• Clinical Rating Scale• Alzheimer's Disease Assessment Scale – Cognitive Subscale
Memory
<i>Word-List Recall</i>
<ul style="list-style-type: none">• Hopkin Verbal Learning Test• California Verbal Learning Test• Rey Auditory Verbal Learning Test• Selective Reminding Test
<i>Narrative Memory</i>
<ul style="list-style-type: none">• Wechsler Memory Scale – Logical Memory• Rivermead Behavioural Memory Test – Story Recall
<i>Non-Verbal</i>
<ul style="list-style-type: none">• Wechsler Memory Scale – Visual Reproduction• Rey Complex Figure Test• Brief Visuospatial Memory Test
Executive Function
<ul style="list-style-type: none">• Delis–Kaplan Executive Function System – Trail Making, Verbal Fluency, Design Fluency, Colour-Word Interference, Sorting, Tower• Wisconsin Card Sorting Test
Visuospatial Function
<ul style="list-style-type: none">• Wechsler Adult Intelligence Scale – Matrix Reasoning, Block Design• Judgement of Line Orientation• Clock Drawing Test• Rey Complex Figure Test – Copy• Clock Drawing Test• Visual Object and Space Perception Battery• Birmingham Object Recognition Battery
Attention and Processing Speed
<ul style="list-style-type: none">• Wechsler Adult Intelligence Scale – Digit Span, Symbol Search, Coding• Digit Symbol Modalities Test• Cancellation Test• Trail Making Test-Part A• Wechsler Memory Scale – Symbol Span
Language
<ul style="list-style-type: none">• Boston Naming Test• Controlled Oral Word Association Test• Token Test

2.5.1 *Measures of Global Cognitive Status*

Brief mental status examinations, such as the Mini-Mental State Examination (MMSE), are often insensitive to the detection of early impairment. In contrast, the Montreal Cognitive Assessment has been suggested as a more useful measure of MCI. The Clinical Dementia Rating (CDR) scale, a semi-structured interview with the patient and the caregiver, is another scale that is commonly used for individuals with MCI. In addition, the Alzheimer's disease Assessment Scale – Cognitive Subscale (ADAS-Cog) has also increasingly been used for MCI, and shown good sensitivity and specificity for differentiating MCI from healthy controls and AD (Verma et al., 2015). In contrast, the Dementia Rating Scale-2 (DRS-2) has a ceiling effect in MCI, making it difficult to distinguish normal ageing from early cognitive decline (De Jager & Budge, 2005), but has demonstrated excellent discrimination of patients of advanced dementia (Jurica, Leitten, & Mattis, 2001). These instruments are often used as screening instruments and will invariably need to be supplemented by more detailed testing to differentiate MCI from dementia and health controls.

2.5.2 *Memory*

As notes earlier in this chapter, impairment in memory is most commonly seen in MCI patients who subsequently progress to a diagnosis of AD dementia. Research studies have shown that there are a variety of memory tests that are useful for identifying those MCI patients who have a high likelihood of progressing to AD dementia within a few years

(Nelson & O'Connor, 2008; Rabin et al., 2009). These tests vary in complexity (i.e., short stories vs. word lists; simple visual designs vs. complicated visual figures), modality of presentation (i.e., visual vs. auditory) and linguistic demand (i.e., geometric shapes vs. words). Tests of episodic memory often consist of an immediate and delayed recall conditions, making it possible to determine retention over a delay. Word-list learning tests, involving learning across multiple trials, has been suggested as perhaps the most challenging and sensitive measures of episodic memory when used to assess early cognitive changes in MCI and AD (Rabin et al., 2009). A different type of verbal memory test focuses on memory for narrative information (e.g., Logical Memory, Story Recall), and in these tests participants are asked to learn and retain a short story. Tests of non-verbal memory may require the participant to study and later reproduce figural drawings and/or to study (e.g., Rey Complex Figure Test).

2.5.3 *Executive Function*

Executive functions comprise interference control, initiation/inhibition, set-shifting, cognitive flexibility, planning, organisation, and abstract reasoning. Some studies have suggested that poor initial performance on measures of executive function were better predictors of AD than tests of episodic memory (Rapp & Reischies, 2005). Recent results from the Alzheimer's disease Neuroimaging Initiative indicated that executive impairments (Trail Making Test B-A difference score, and Digit Symbol Coding) predicated impairments in activities of daily living and in MCI who progressed to AD

(Marshall et al., 2011). More recently, Clark et al. (2012) showed that measures of executive function differentiated between MCI participants who displayed cognitive decline over 12 months from those who did not decline.

2.5.4 *Visuospatial Function*

Visuospatial impairments are often among the first symptoms noted in AD (Mandal, Joshi, & Saharan, 2012; Weintraub, Wicklund, & Salmon, 2012) and can be manifested by individuals as getting lost in familiar environments, forgetting where they placed their personal items, or difficulty driving or parking a car (Quental, Brucki, & Bueno, 2013). Visuospatial assessment often includes measures of visual orientation (e.g., Judgement of Line Orientation), visual perception (e.g., Silhouettes), visual analysis and synthesis (e.g., Matrix Reasoning), and visuoconstructive skills (e.g., Block Design, Rey Complex Figure Test - Copy) (Possin, 2010; Rizzo, Anderson, Dawson, & Nawrot, 2000; Salmon & Bondi, 2009).

2.5.5 *Attention and Processing Speed*

Attention and processing speed are basic cognitive processes that sub-serve many other higher-order cognitive domains. Tasks of attention and processing speed vary widely in length and complexity. The most basic aspect of attention pertains to attention span – the amount of information that an individual can hold in mind at one time. Auditory attention

span is often assessed by having the patient repeat progressively longer series of digits (e.g., Digit Span), whereas visual attention span is assessed by having the participant point to a series of locations indicated by the examiner on a spatial array (e.g., Symbol Span). Other tasks of attention focus on capacity of sustained vigilance or continuous performance (e.g., Cancellation). Processing speed tests typically involve the ability to quickly perform relatively easy or over-learned cognitive tasks. Johnson, Storandt, Morris, and Galvin (2009) reported that tests of attention and processing speed (Digit Symbol and Trail Making Test-Part A) demonstrated an inflection point 3 years before clinical diagnosis of AD, whereas the inflection point for verbal memory was not seen until 1 year before clinical diagnosis, suggests that perhaps attention and processing speed deficits occur before episodic memory deficits.

2.5.6 *Language*

A core component of the evaluation of the MCI individuals is the assessment of language. Language abilities can be assessed formally using standardised neuropsychological tests or informally throughout the assessment. Conversation speech is rated in terms of fluency, comprehension, and word findings problems (Graham, Cully, Snow, Massman, & Doody, 2004). Standardised cognitive tests are often in the form of confrontation naming (e.g., Boston Naming) and language comprehension (e.g., Token Test) (Nelson & O'Connor, 2008).

2.5.7 *Defining Impairment*

More recently, MCI studies have begun to explore the requirement used to define 'impairment', specifically the number of impaired test results required to meet criteria in a given cognitive domain (e.g., 1 test vs. 2 tests) and the predetermined cut-off points to identify cognitive impairment (e.g., 1.0, 1.5 or 2SD below the normative mean). In the original MCI criteria, Petersen et al. (1999) suggested a cut-off of at least 1.5SD below the age- and education-adjusted values. However, a number of studies have defined MCI on the basis of cognitive impairment of 1.0SD below the average score of normal elderly subjects (Lonie et al., 2010; Ritchie et al., 2001), while others used the 10th percentile (equivalent to -1.3SD) as the cut-off (Mitchell et al., 2009; Summers & Saunders, 2012). Some studies used a more conservative cut-off of 2SD lower than the norm (De Ronchi et al., 2005). Several studies have indicated that those with more severe cognitive deficits, defined by either the number of impaired tests or level of performance, are at increased risk for developing dementia. Loewenstein et al. (2009) provided compelling data that MCI diagnoses based on the requirement of two or more tests within a single domain, are superior to those based on a single impaired score. These authors reported that if one test was used to diagnose MCI, 56% of the individuals improved, 25% remained stable, and 19% decline over a two- to three-year period. In contrast, if two impaired scores in a domain were required, none of these individuals showed improvements over the same follow-up period, 50% remained stable, and 50% declined. The 'two tests within a single domain' approach was further validated by Jak et al. (2009). In their study, 73 non-demented, neurologically normal, community-dwelling older adults were followed up for

18 months. At baseline and follow-up participants were classified as either normal or as having MCI by means of different diagnostic criteria, which varied on the number of neuropsychological tests considered in the diagnosis and the cut-off for objective cognitive impairment. Examination of classification agreement across time with different strategies revealed that the most conservative strategy examined for diagnosing MCI, that is, requiring performance on two measures within one cognitive domain equal to or greater than 1.5SD below the normative mean on two measures within a domain, had the greatest reliability and stability of diagnosis (Jak et al., 2009). Remarkably, the conservative strategy (two tests at -1.5SD) showed significant associations with apolipoprotein E (APOE) genotype and medial temporal atrophy (Schinka et al., 2010). The studies reviewed suggest that a more comprehensive approach in neuropsychological assessment coupled with a lower cut-off value may be the better choice for researchers looking for a more stable diagnostic strategy.

2.6 The Current Study

The overarching goal of the current study was to slow down the progression to AD, thus amnesic subtype became the obvious subtype to focus on, given its higher conversion rate to AD compared with the non-amnesic subtype. To accurately identify aMCI, a comprehensive battery of neuropsychological tests was adopted by the current study. Tests were classified into five broad cognitive domains (memory, attention and processing speed, language, visuospatial skills, and executive function) each with at least

two tests within each domain. The 1.5SD below normative data was adopted as the cut-off value to indicate impairment, alongside the requirement that two or more tests within the memory domain to contribute to the classification aMCI.

CHAPTER 3 - Cognitive Screening for MCI

3.1 Introduction

As mentioned earlier, it is of value to detect and diagnose MCI because people with this condition are at increased risk for AD and other types of dementia compared with similarly aged individuals in the general population (Petersen & Morris, 2005). One of the major challenges in cognitive testing is to provide abbreviated tests to differentiate MCI from normal cognition. As mentioned in Chapter 2, the diagnosis of MCI requires a comprehensive assessment of cognition (Winblad et al., 2004). However, time and resources are often limited in clinical and research settings, and comprehensive neuropsychological assessment is not always feasible. The usefulness of a particular screening tool lies in its diagnostic and statistical robustness – ideally, high sensitivity and specificity along with high accuracy for positive predictive value (PPV) and negative predictive value (NPV). Sensitivity refers to the ability of a test to correctly classify an individual as impaired; specificity refers to ability of a test to correctly classify an individual as unimpaired (Florkowski, 2008). PPV refers to the proportion of people with a positive test who actually have the disorder; and NPV refers to the proportion of those with a negative test who do not have the disease (Florkowski, 2008). Sensitivity and specificity of a particular measure may vary depending on the mix of participants and in particular the inclusion of people who are difficult to diagnose, while PPV and NPV are

directly related to the prevalence of the disease in the population. Assuming sensitivity and specificity remain the constant, the PPV will increase with increasing prevalence; and NPV decreases with increase in prevalence (Florkowski, 2008).

A number of screening instruments have been used in clinical care and research to identify global cognitive impairment. The Montreal Cognitive Assessment (MoCA) is becoming one of the most widely used cognitive screens to assess cognitive status. While prior research has demonstrated the superiority of MoCA over Mini-Mental State Examination (MMSE) in differentiating the MCI cases, the specificity of the MoCA for MCI in the general population has been reported by some studies as poor (McLennan, Mathias, Brennan, & Stewart, 2011; T. Smith et al., 2007). Hence, additional tools may be valuable to screen for MCI.

Longitudinal studies suggest that AD is preceded by decline in multiple cognitive functions (R. S. Wilson, Leurgans, Boyle, & Bennett, 2011). Decline in visuospatial function and speeded psychomotor skills, in addition to episodic memory deficits, have been suggested as the earliest signs of prodromal AD (Backman, Jones, Berger, Laukka, & Small, 2005; Grober et al., 2008; R. S. Wilson et al., 2011). One longitudinal study compared individuals who became demented during follow-up and people who remained non-demented and reported that tests of speeded processing of visual information were the most significant predictors of which individuals will subsequently develop dementia (Johnson et al., 2009). Therefore, in addition to the MoCA, the current study included the

Rey Complex Figure Test (RCFT) and the Trail Making Test Part A (TMT-A) as part of a brief cognitive screen. The RCFT was chosen because it measures both visuospatial abilities and visuospatial memory. Although not a screening instrument, its copy and immediate recall (3min) component takes minimal time to administer. Part A of the TMT is another brief test of visuospatial skills combined with speed of processing. Galvin et al. (2005) demonstrated in their longitudinal study that TMT-A was the only baseline cognitive measure that predicted dementia, with individuals who were slower on this measure developing dementia sooner.

The objective of this chapter was to compare the diagnostic utility of the MoCA, RCFT and TMT-A in identifying people with MCI, and whether additional diagnostic value is achieved by combining these measures.

3.2 Method

3.2.1 *Brief Cognitive Screening*

Between 2010 and 2011, 609 people aged 65 or older were recruited in the Canterbury region through newspaper advertisements, and through public seminars made to community groups, residential homes and through the New Zealand Brain Research Institute (NZBRI) database. These community volunteers were given a short screen at the participant's home or at the NZBRI, in a single 30-minute session. Participants were assessed by psychology students, including the author, trained in administering the

neuropsychological tests. The screen consisted of the MoCA (Nasreddine et al., 2005), RCFT Copy (Meyers & Meyers, 1995), RCFT Recall (3-min delay) (Meyers & Meyers, 1995), and TMT-A (Mitrushina, Boone, Razani, & D'Elia, 2005). Demographic characteristics of the screening sample are presented in Table 3-1.

Table 3-1
Demographic Characteristics of the Screening Sample; Mean (SD)

Screening Participants (n = 609)	
Age	74.2 (6.2)
Gender (F:M)	387: 222
Education	12.9 (2.6)
Ethnicity	605 NZ European; 4 Maori, two of whom indicated both Maori and NZ European ethnicity

Of the 609 assessed participants, 222 were excluded on the basis of: aged 85 years or older; previous or current medical complications (i.e., multiple sclerosis, Parkinson's disease, major coronary disease, stroke, cancer); developmental disorders (i.e., learning disability, autistic spectrum disorder); major psychiatric conditions (i.e., schizophrenia, bipolar); or current medications (i.e., antidepressants, benzodiazepines) that are likely to affect cognitive functioning. Other reasons for exclusion are provided in Figure 3-1.

3.2.2 Initial Participant Classification

The remaining 387 participants were classified into three categories: Probable MCI ($n = 75$), Possible MCI ($n = 72$) and Probable Healthy Control (Probable HC; $n = 240$) based on their performance on the MoCA, TMT-A, RCFT Copy and RCFT Recall (Table 3-2). As progression to AD is associated with both memory impairment and decline in non-

memory domains, participants in the Probable MCI group had to meet one of the following criteria: either a MoCA score of < 28 , but an impaired score on RCFT Recall ($< -1.5SD$; 0.7th percentile) or a poor performance on the MoCA (< 26 ; Nasreddine et al., 2005) plus a borderline impaired or worse score on any one of the three measures ($< -1.3SD$; 10th percentile). People in the Probable HC group were deemed likely to be ageing normally, if they either attained a MoCA score of > 25 and above ‘borderline’ performance on all other tests ($> -1.3SD$; 10th percentile) or had relatively poor performance on MoCA (< 26), but ‘normal’ performance on all other tests ($> 0.7SD$; 25th percentile). The Possible MCI group consisted of individuals with variable test performance who did not meet either the Probable HC or Probable MCI criteria.

Table 3-2

Preliminary Classification Criteria Based on the Brief Neuropsychological Screen

Group	Specific criteria
Probable MCI	MoCA < 26 ; any z-score $< -1.3SD$ ($n = 64$); or MoCA < 28 ; RCFT Recall $< -1.5SD$ ($n = 11$)
Possible MCI	MoCA < 26 ; all z-scores $> -1.3SD$, but $< -0.7SD$ ($n = 28$); or MoCA > 25 but < 28 ; any z-score $< -1.3SD$, but RCFT Recall $> -1.5SD$ ($n = 20$); or MoCA > 27 ; any z-score $< -1.3SD$ ($n = 24$)
Probable HC	MoCA > 25 ; all z-scores $> -1.3SD$ ($n = 103$); or MoCA < 26 ; all z-scores $> -0.7SD$ ($n = 137$)

Note. A z-score of -1.3 is equivalent to the 10th percentile which is often used to indicate ‘borderline’ performance. A z-score of -0.7 is equivalent to the 25th percentile which is often used to indicate the beginning of ‘low average’ range. MoCA = Montreal Cognitive Assessment; RCFT = Rey Complex Figure Test; MCI = Mild Cognitive Impairment; HC = Healthy Control; SD = Standard Deviation.

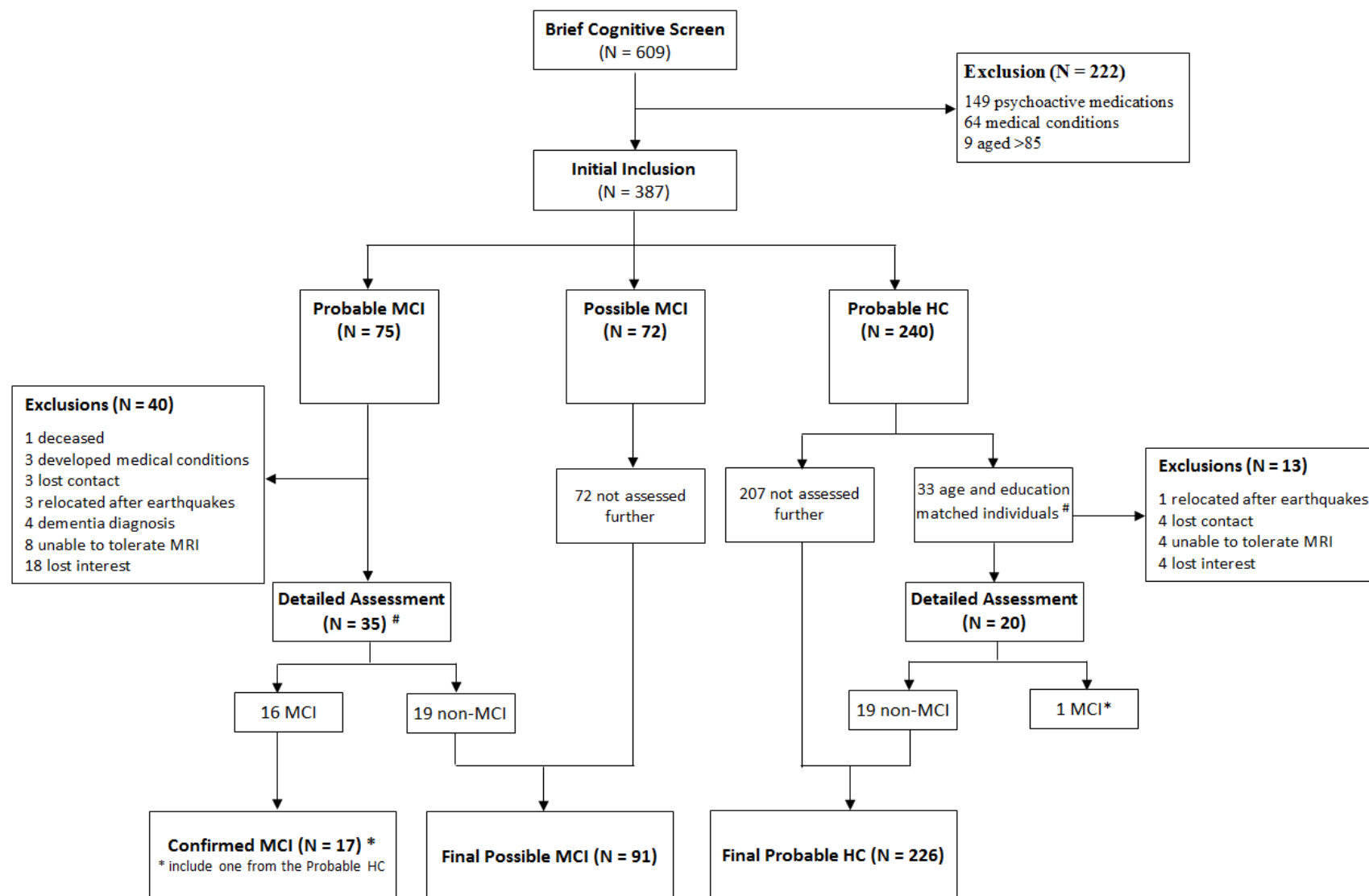


Figure 3-1. Flow diagram of participation. HC = Healthy Controls; MCI = Mild Cognitive Impairment.

*Final MCI = 17, including one MCI from the Probable HC group.

Probable HC individuals ($n = 33$) were aged and education matched to the 35 individuals of the Probable MCI group.

3.2.3 *Detailed Neuropsychological Assessment*

Subsequent to the cognitive screen, all Probable MCI who could be examined ($n = 35$) and, for comparison, an age and education matched subgroup of Probable HC ($n = 20$) received detailed neuropsychological assessment at NZBRI to confirm their cognitive status (Figure 3-1). Neuropsychological tests were administered in a fixed sequence with tests divided across two sessions. Verbal tests were intermingled with non-verbal tests in each session to reduce fatigue and test contamination. For example, non-verbal (non-memory) tests were administered between the immediate and delayed recall trials of verbal memory test, and vice versa. For each neuropsychological test, age-matched normative data were used to ascertain whether performance was within the normal range or below the normal range. Three postgraduate psychology students including the author administered the tests.

The tests included measures of (1) premorbid IQ (Advanced Clinical Solution; Wechsler, 2009); (2) global cognitive functioning – MoCA (Nasreddine et al., 2005); Dementia Rating Scale (DRS-2; Jurica et al., 2001); Alzheimer’s Disease Assessment Scale-Cognition (ADAS-cog; D. P. Graham et al., 2004; Mohs et al., 1997); (3) learning and memory – California Verbal Learning Test-II Short Form (CVLT-II SF; Delis, Kramer, Kaplan, & Ober, 2000); Brief Visuospatial Memory Test-Revised (BVM-T-R; Benedict, 1997); RCFT Immediate and Delayed Recall (Meyers & Meyers, 1995); Story Recall (Wilson et al., 2008); Rappel Indice 48 Items (RI-48; Adam et al., 2007); Visual

Association Test (Lindeboom & Schmand, 2003; Lindeboom, Schmand, Tulner, Walstra, & Jonker, 2002); (4) executive function – Stroop Interference (Delis et al., 2000); Letter Fluency (Delis et al., 2000); Category Fluency (Delis et al., 2000); Category Switching (Delis et al., 2000); Action Fluency (Piatt, Fields, Paolo, & Troster, 2004); Design Fluency (Delis et al., 2000); TMT-B (Mitrushina et al., 2005); (5) attention and processing speed – Digit Span Test (Wechsler, 2008a, 2008b); Stroop Word Reading (Delis et al., 2000); Stroop Colour Naming (Delis et al., 2000); Symbol Digit Modality Test (SDMT; Smith, 1982); TMT-A (Mitrushina et al., 2005); (6) visuospatial skills – RCFT Copy (Meyers & Meyers, 1995); Matrix Reasoning (Wechsler, 2008a, 2008b); Judgement of Line Orientation (Benton, Hamsher, Varney, & Spreen, 1983); Silhouettes (Warrington & James, 1991); and (7) language – Boston Naming (Lansing, Ivnik, Cullum, & Randolph, 1999); Token Test (Unverzagt et al., 1999). Subjective cognitive impairment was determined by asking the participant and informant “Do you have problems with memory or thinking?” Activities of daily living were measured using the Clinical Dementia Rating (CDR; Morris, 1993). The CDR and DRS-2 were used to exclude dementia. Tests used in the detailed neuropsychological assessment are described in Appendix A.

3.2.4 *Final Participant Classification*

Following the flowchart described in Figure 3-1, participants were assigned to their final groups, adjusted on the basis of performance on the detailed neuropsychological

assessment where available. As a result, 17 individuals were classified as MCI using Petersen recommendations (Petersen, Doody, et al., 2001): the presence of (1) objective evidence of cognitive decline on two or more memory tests, defined as lower than age adjusted norms at 1.5SD below the standardised mean or an equivalent ‘impaired score’ on the Story Recall – a borderline profile score of 1 (borderline) or a score of < 19 on RI-48 delayed recall; (2) a global cognitive score of either MoCA < 26 or DRS-2 scaled score < 9; (3) subjective memory complaint, by participant or informant; and (4) essentially preserved activities of daily as shown by a total CDR of 0 or 0.5.

Participants who received detailed assessment but failed to meet these confirmatory MCI criteria either remained as Probable HC or were reclassified as Possible MCI. Reclassification to Possible MCI was necessary when their performance on the standardised neuropsychological tests was not sufficient for a classification of Probable HC. All participants who did not receive detailed neuropsychological testing remained with the classification given after screening. Table 3-3 provides the demographic characteristics of the three cognitive groups, there were no significant differences across the three groups in terms of age, gender, education or ethnicity.

Table 3-3
Demographics Characteristics of the Three Cognitive Groups

	Confirmed MCI (n = 17)	Possible MCI (n = 91)	Probable HC (n = 275)
Age	74.5 (4.6)	74.0 (6.1)	72.8 (5.4)
Gender	7 : 10	59 : 32	139 : 88
Education	12.9 (2.8)	13.1 (2.7)	13.4 (2.6)
Ethnicity	1 Maori (both Maori & NZ European)	All NZ European	2 Maori

Note. MCI = Mild Cognitive Impairment; HC = Healthy Control. No significant differences.

3.2.5 *Diagnostic Utility of Individual Screening Tests*

The initial receiver operating characteristic (ROC) analyses examined the diagnostic utility of each individual screening measure, namely the MoCA, RCFT Copy, RCFT Recall, and TMT-A. The cut-off that produced the highest Youden index (sensitivity + specificity – 1) was identified. A prevalence rate of 15% for MCI was chosen to compute positive and negative predictive values (Ritchie, 2004). These univariate ROC analyses were performed with MedCalc version 13.1.2 (www.medcalc.be). Three separate ROC analyses were carried out:

1. For the first analysis, the Possible MCI and the Probable HC were treated as a single non-MCI group ($n = 317$) and compared with the Confirmed MCI group ($n = 17$). Individuals included in this analysis provided a good representation of the general elderly population, where individuals exhibited a range of cognitive functioning. Therefore, cut-off values generated from this analysis should be considered when making MCI diagnosis in the general elderly population.
2. The second analysis compared the Confirmed MCI group ($n = 17$) with the Probable HC group ($n = 226$). This analysis provides the cut-off values for diagnosing MCI from normal cognition.
3. The third analysis compared the Confirmed MCI group ($n = 17$) with the Possible MCI group ($n = 91$). Results from this analysis should be considered when diagnosing MCI from individuals with some cognitive impairments but not sufficient for a diagnosis of MCI.

3.2.6 *Diagnostic Utility of Combination of Screening Tests*

Multivariate logistic regression analysis was then conducted to investigate whether combinations of the screening instruments improved the detection of MCI. These analyses were carried out in consultation with Associate Professor Christos Nakas at Laboratory of Biometry, University of Thessaly, Magnesia, Greece. For each of the three analysis listed above, a logistic regression model was developed using the four screening measures, and adding demographic variables to adjust for their influence. After model building, the predicted probabilities of each model (referred to as Pscores in Figure 3-3) were used to plot an ROC curve that was tested against the ROC of each individual screening measure. The models were validated using a leave-one-out analysis.

3.2.7 *Comparisons across Three Groups*

Three-Dimensional ROC analysis addresses the performance of a screening measure when making simultaneous discriminations among three groups (Nakas, 2014), in this instance Confirmed MCI, Possible MCI, and Probable HC. ROC surfaces were plotted on three-dimensional coordinates, and the volume under the ROC surface (VUS) indicates the discriminatory power of the screening instruments across all three groups simultaneously. The VUS is a logical extension of the traditional two-dimensional area under the curve in the two-group comparison and is appropriate when the dependent variable can be expected to produce an ordinal arrangement across the three groups. These analyses were conducted by Associate Professor Christos Nakas, in consultation

with the current author, and the results were assessed through ROC surface analysis along the lines described in Nakas (2014) and J. L. Li and Zhou (2009).

3.3 Results

3.3.1 *Confirmed MCI vs. non-MCI (Possible MCI and Probable HC combined)*

The first set of analyses was conducted to examine the diagnostic utility of the different screening tests to differentiate confirmed MCI from non-MCI (Possible MCI and Probable HC combined). The optimal cut-off point, sensitivity, specificity, PPV and NPV for each screening instrument are listed in Table 3-4. The MoCA, RCFT Copy and RCFT Recall produced high AUCs in discriminating individuals with MCI from those without MCI, and were significantly superior in this regard compared to the AUC for TMT-A (AUC difference of 26.1% for the MoCA, $p < 0.001$; AUC difference of 23.5% for the RCFT Copy, $p < 0.01$; and AUC difference of 34.4% for the RCFT recall, $p < 0.001$). The RCFT Recall appeared to perform better than the MoCA and the RCFT Copy in the discriminating MCI from non-MCI. The AUC for the RCFT Recall was significantly larger than that shown by the MoCA (AUC difference = 8.25%, $p < 0.05$), but just failed to reach significance when compared to RCFT Copy (AUC difference = 10.9%, $p = 0.05$). The AUC difference between the MoCA and RCFT Copy did not reach significance (AUC difference = 2.64%, $p = 0.58$).

Table 3-4

Confirmed MCI vs. non-MCI: Diagnostic Performance of MoCA, RCFT Copy, RCFT Recall, TMT-A

	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)	p-value
MoCA	<26	88.24 (63.6 to 98.5)	67.51 (62.0 to 72.6)	32.4 (24.6 to 40.9)	97.0 (93.6 to 98.9)	0.83 (0.78 to 0.87)	<0.001
RCFT Copy	<-0.82	70.59 (44.0 to 89.7)	78.55 (73.6 to 82.9)	36.7 (27.1 to 47.2)	93.8 (89.9 to 96.5)	0.80 (0.76 to 0.84)	<0.001
RCFT Recall	<-1.10	82.35 (56.6 to 96.2)	86.12 (81.8 to 89.7)	51.1 (39.8 to 62.4)	96.5 (93.4 to 98.4)	0.91 (0.88 to 0.94)	<0.001
TMT-A	<1.03	88.24 (63.6 to 98.5)	33.86 (28.7 to 39.4)	19.1 (14.2 to 24.7)	94.2 (87.8 to 97.9)	0.57 (0.51 to 0.62)	0.31
Combination Model		94.12 (71.3 to 99.9)	89.59 (85.7 to 92.7)	61.5 (49.7 to 72.4)	98.9 (96.7 to 99.8)	0.94 (0.91 to 0.96)	<0.001

Note. MoCA = Montreal Cognitive Assessment; RCFT = Rey Complex Figure Test; TMT = Trail Making Test; Combined Model = MoCA + RCFT Copy + RCFT Recall; cut-off = the value that produced the highest Youden index; PPV = Positive Predictive Value; NPV = Negative Predictive Value; AUC = Area Under the Curve; CI = Confidence Interval.

Logistic regression determined the combination of tests that produced the best discriminant ability of the Confirmed MCI and the non-MCI. This analysis suggested that the optimal combination was produced by the inclusion of the MoCA, RCFT Copy and RCFT Recall (but not TMT-A). As illustrated in Figure 3-2, the AUC for the combination model was higher than the AUC obtained by using a single measure, with a significant difference relative to the MoCA (AUC difference = 11.0%; $p < 0.001$) and the RCFT Copy (AUC difference = 13.7%; $p < 0.001$). However, the difference failed to reach significance when compared to the RCFT Recall (AUC difference = 2.78%; $p = 0.22$), although sensitivity and PPV were increased by the combination model compared to the RCFT Recall.

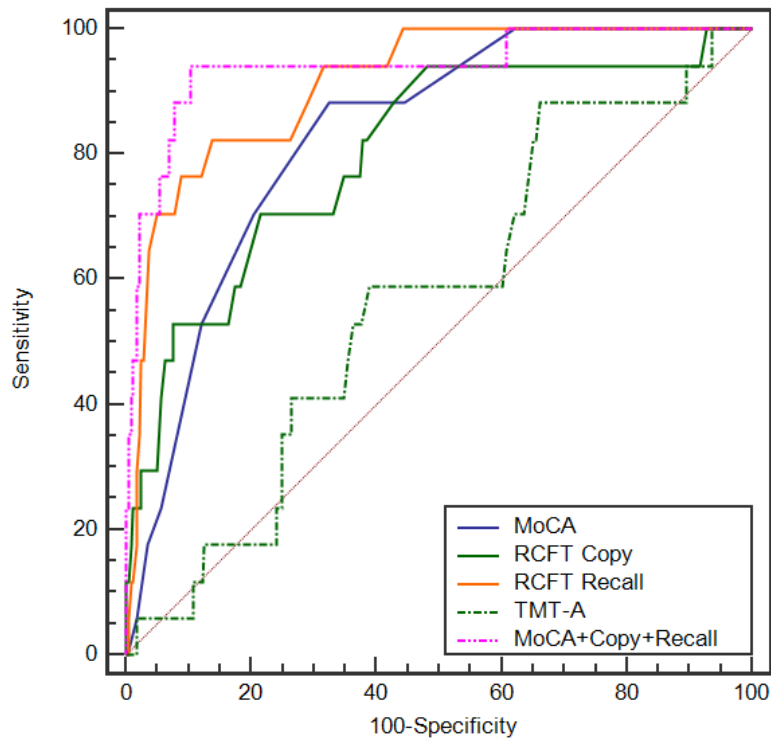


Figure 3-2. ROC curves for MoCA, RCFT Copy, RCFT Recall, TMT-A and the combination model to detect Confirmed MCI vs. non-MCI.

The logistic regression model was then used to determine the cut-off values for differentiating the Confirmed MCI from non-MCI, using the combination of MoCA, RCFT Copy and RCFT Recall. MoCA is often used by itself in previous literature, but here cut-offs of the added RCFT measures for different MoCA scores are presented. Figure 3-3 provides the visual representations of four example of MoCA scores and the respective cut-off values for RCFT Copy and RCFT Recall for diagnosing Confirmed MCI vs. non-MCI. Refer to Appendix B for more detailed information on cut-off scores. For simplicity, cut-off values were presented as cross-tabulation tables of RCFT Copy and RCFT Recall for relevant MoCA scores of 15 through to 30. For example, a person

with a MoCA of 28, RCFT Copy of -1.5SD and RCFT Recall of -1.5SD would be classified as MCI. In Contrast, a person with a lower MoCA score of 19, but a RCFT Copy of 0.7 and RCFT Recall of 0.1 would be classified as non-MCI, according to the model.

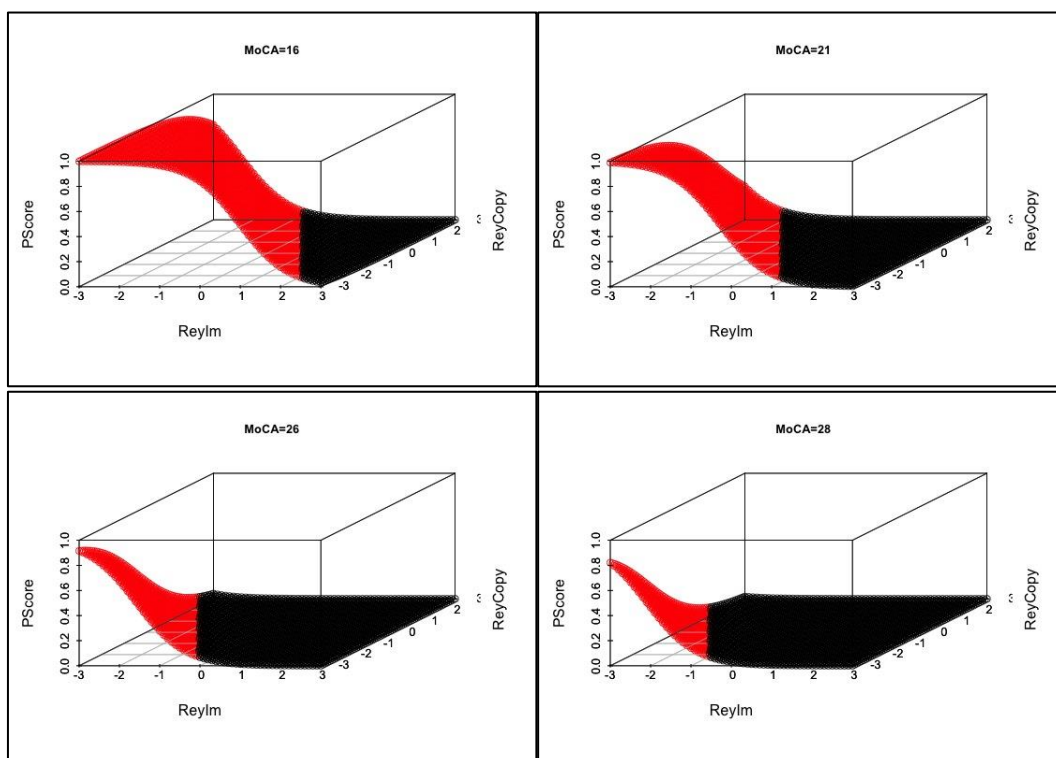


Figure 3-3. Three-dimensional logistic regression graphs showing cut-off values for RCFT Copy and Recall for a range of MoCA scores. Figure courtesy of Associated Professor Christos Nakas. *P*-scores on the *z*-axis represents the predicted probabilities based on the logistic regression model according to the MoCA score on the title and the RCFT Copy and Recall scores on the *x* and *y* axes, respectively. *x*-axis represents the *z*-score range for RCFT Recall, and *y*-axis represent the *z*-score range for RCFT Copy. Red = MCI; Black = non-MCI.

3.3.2 Confirmed MCI vs. Probable HC

When discriminating Confirmed MCI from Probable HC, a similar profile emerged, with the MoCA, RCFT Copy and RCFT Recall producing high AUCs that were superior to the TMT-A in discriminating MCI from Probable HC. The optimal cut-off point, sensitivity and specificity, PPV and NPV for each screening instrument are listed in Table 3-5. The AUC for the RCFT recall was significantly higher than that shown by the MoCA (AUC difference of 10.1%; $p < 0.01$), but failed to reach significance when compared with RCFT Copy (AUC difference of 8.31%; $p = 0.07$). The MoCA and the RCFT Copy had similar AUCs (AUC difference of 1.78%, $p = 0.68$); while the MoCA appeared to be a more sensitive measure, the RCFT Copy was more specific and had a higher PPV than the MoCA (Table 3-5).

Table 3-5
Confirmed MCI vs. Probable HC: Diagnostic Performance of MoCA, RCFT Copy, RCFT Recall, TMT-A

	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)	p-value
MoCA	<26	88.24 (63.6 to 98.5)	73.01 (66.7 to 78.7)	36.6 (26.6 to 47.5)	97.2 (93.3 to 99.2)	0.86 (0.81 to 0.90)	<0.001
RCFT Copy	<-0.82	70.59 (44.0 to 89.7)	94.25 (90.4 to 96.9)	68.4 (51.2 to 82.6)	94.8 (90.8 to 97.4)	0.88 (0.84 to 0.92)	<0.001
RCFT Recall	<-1.10	82.35 (56.6 to 96.2)	97.35 (94.3 to 99.0)	84.6 (68.5 to 94.4)	96.9 (93.5 to 98.8)	0.96 (0.93 to 0.98)	<0.001
TMT-A	<1.03	88.24 (63.6 to 98.5)	34.67 (28.5 to 41.3)	19.2 (13.6 to 26.1)	94.3 (86.5 to 98.4)	0.58 (0.51 to 0.64)	0.28
Combination Model		94.12 (71.3 to 99.9)	100 (98.4 to 100)	100 (89.8 to 100)	99.0 (96.5 to 99.9)	0.97 (0.94 to 0.99)	<0.001

Note. MoCA = Montreal Cognitive Assessment; RCFT = Rey Complex Figure Test; TMT = Trail Making Test; Combined Model = MoCA + RCFT Copy + RCFT Recall; Cut-off = the value that produced the highest Youden index; PPV = Positive Predictive Value; NPV = Negative Predictive Value; AUC = Area Under the Curve; CI = Confidence Interval.

The combination model showed excellent AUC, sensitivity, specificity, PPV and NPV. Consistent with the Confirmed MCI vs. non-MCI comparisons, the AUC for the Confirmed MCI vs. Probable HC produced by the combination model was excellent and higher than the AUC obtained by using single measures (Figure 3-4). A significant improvement of the combined model was found relative to the MoCA (AUC difference = 10.8%; $p < 0.001$) and the RCFT Copy (AUC difference = 9.01%; $p < 0.01$). Once again, the AUCs for the combined model and the RCFT Recall were similar (AUC difference = 6.93%, $p = 0.68$). Cut-off values for differentiating Confirmed MCI from Probable HC are presented as cross-tabulation tables in Appendix C.

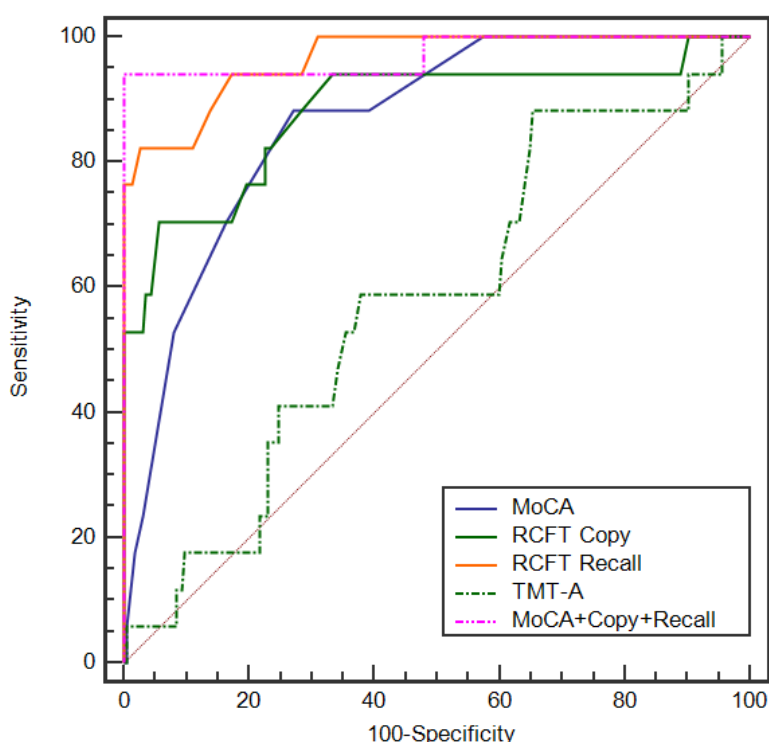


Figure 3-4. ROC curves for MoCA, RCFT Copy, RCFT Recall, TMT-A and the combination model to detect Confirmed MCI vs. Probably HC.

3.3.3 Confirmed MCI vs. Possible MCI

Given this more difficult discrimination, the AUCs were smaller than for the previous comparisons. When discriminating the Confirmed MCI from Possible MCI, only the MoCA and RCFT Recall produced significant AUCs. In contrast to previous comparisons, the RCFT Copy provided non-significant AUC (Table 3-6). The AUC for the MoCA and RCFT Recall were significant higher than that shown by the TMT-A (AUC difference = 20% for the MoCA, $p < 0.01$; AUC difference = 23.7%, $p < 0.01$), but the failed to reach significance when compared to RCFT Copy (AUC difference of 13.6% for MoCA, $p = 0.10$; AUC difference of 17.3% for RCFT Recall, $p = 0.11$). While RCFT Recall and the MoCA showed similar AUC values (AUC difference of 3.68%; $p = 0.61$), the RCFT was a more specific measure than the MoCA.

Table 3-6
Confirmed MCI vs. Possible MCI: Diagnostic Performance of MoCA, RCFT Copy, RCFT Recall, TMT-A

	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)	p-value
MoCA	<26	88.24 (63.6 to 98.5)	53.85 (43.1 to 64.4)	25.2 (14.6 to 38.5)	96.3 (86.9 to 99.6)	0.74 (0.65 to 0.82)	<0.001
RCFT Copy	<-1.53	52.94 (27.8 to 77.0)	73.63 (63.3 to 82.3)	26.2 (12.4 to 44.4)	89.9 (80.7 to 95.6)	0.61 (0.51 to 0.70)	0.21
RCFT Recall	<-1.5	70.59 (44.0 to 89.7)	82.42 (73.0 to 89.6)	41.5 (23.2 to 61.7)	94.1 (86.5 to 98.1)	0.78 (0.69 to 0.85)	<0.001
TMT-A	<1.03	88.24 (63.6 to 98.5)	31.87 (22.5 to 42.5)	18.6 (10.6 to 29.1)	93.9 (79.1 to 99.3)	0.54 (0.44 to 0.64)	0.54
Combination Model		70.59 (44.0 to 89.7)	92.31 (84.8 to 96.9)	61.8 (36.8 to 83.0)	94.7 (87.8 to 98.3)	0.86 (0.78 to 0.92)	<0.001

Note. MoCA = Montreal Cognitive Assessment; RCFT = Rey Complex Figure Test; TMT = Trail Making Test; Combination Model = MoCA + RCFT Copy + RCFT Recall; Cut-off = the value that produced the highest Youden index; PPV = Positive Predictive Value; NPV = Negative Predictive Value; AUC = Area Under the Curve; CI = Confidence Interval.

The combination model performed better than the individual screening measures (Figure 3-5). The combined model was significantly superior to the MoCA (AUC difference of 11.8%; $p < 0.05$). A significant difference was also observed between the combined model and the RCFT Copy (AUC difference of 25.4%, $p < 0.001$). Unlike the previous comparisons, the combination model now produced an AUC difference that approached significance for the RCFT Recall (AUC difference of 8.14%, $p = 0.09$), suggesting that an increased sample size might confirm the benefit of the combination model for this discrimination. Cut-off values for are presented in Appendix D.

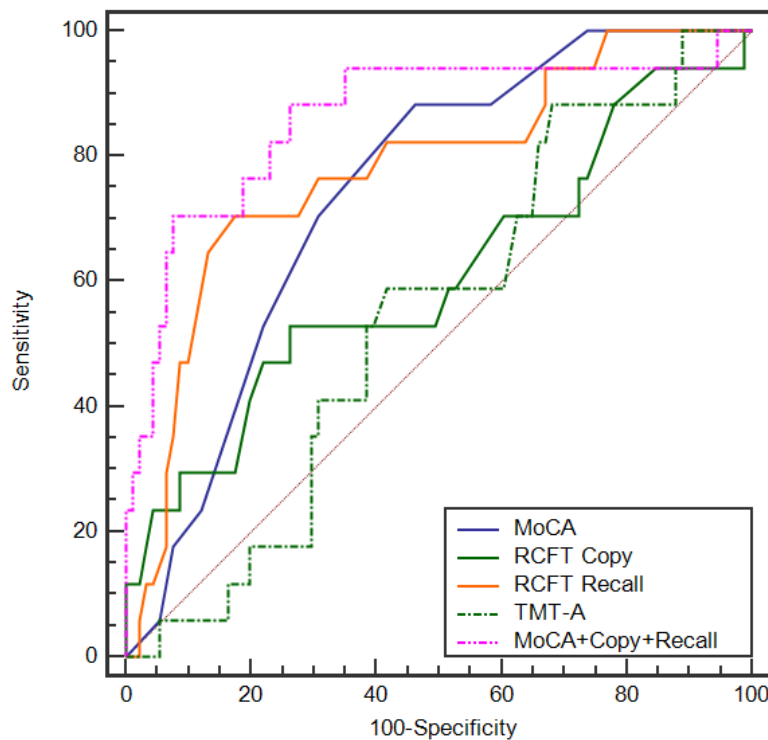


Figure 3-5. ROC curves for MoCA, RCFT Copy, RCFT Recall, TMT-A and the combination model to detect Confirmed MCI vs. Possible MCI.

3.3.4 Three-Dimensional ROC Results

Simultaneous discrimination of the three classes (MCI, Possible MCI, Probable HC) provided further evidence for the superiority of the combined model (VUS = 0.77; 95% CI = 0.64-0.89; Figure 3-6) over the MoCA (VUS = 0.39; 95% CI = 0.31-0.48), the RCFT copy (VUS = 0.48; 95% CI = 0.33-0.62), and now also the RCFT recall (VUS = 0.60; 95% CI = 0.48-0.72; Figure 3-7).

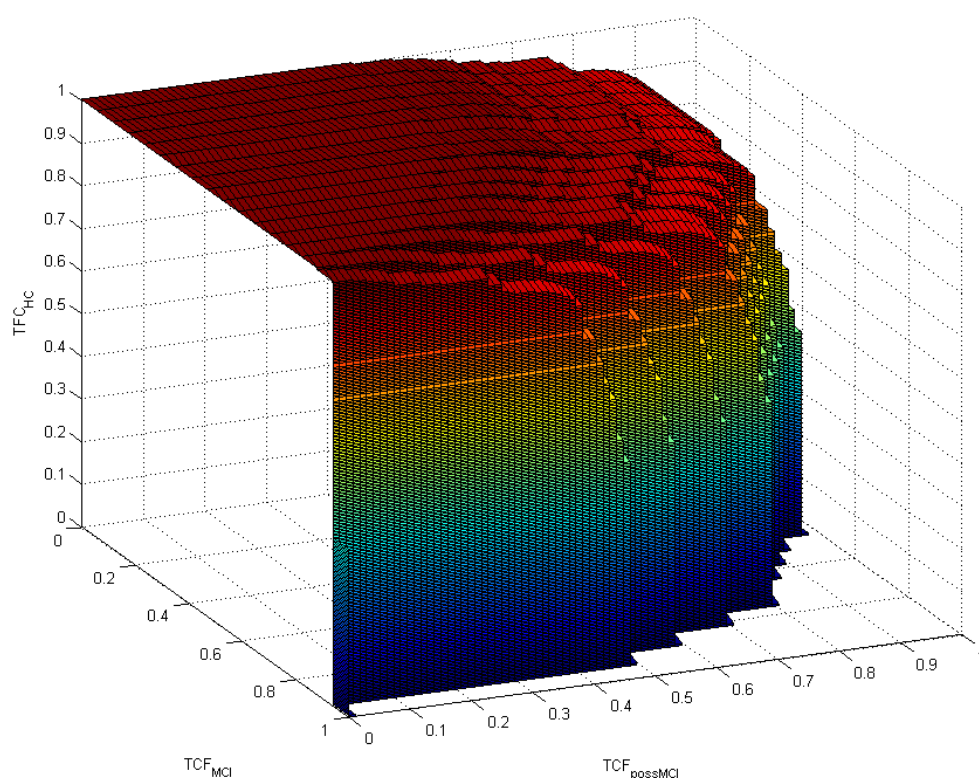


Figure 3-6. Three-dimensional receiver operating characteristic surfaces for the combination model. Figure courtesy of Associated Professor Christos Nakas. MCI = Confirmed MCI; possMCI = Possible MCI; HC = Probable Healthy Control; TFC = True Class Fraction.

Pairwise comparisons showed that each of the individual measures was able to successfully differentiate between the three classes of participants (Table 3-7). The combined model was superior to the individual measures in discriminating the three groups, indicated by good pairwise AUCs when discriminating the otherwise more difficult Confirmed MCI vs. Possible MCI comparison.

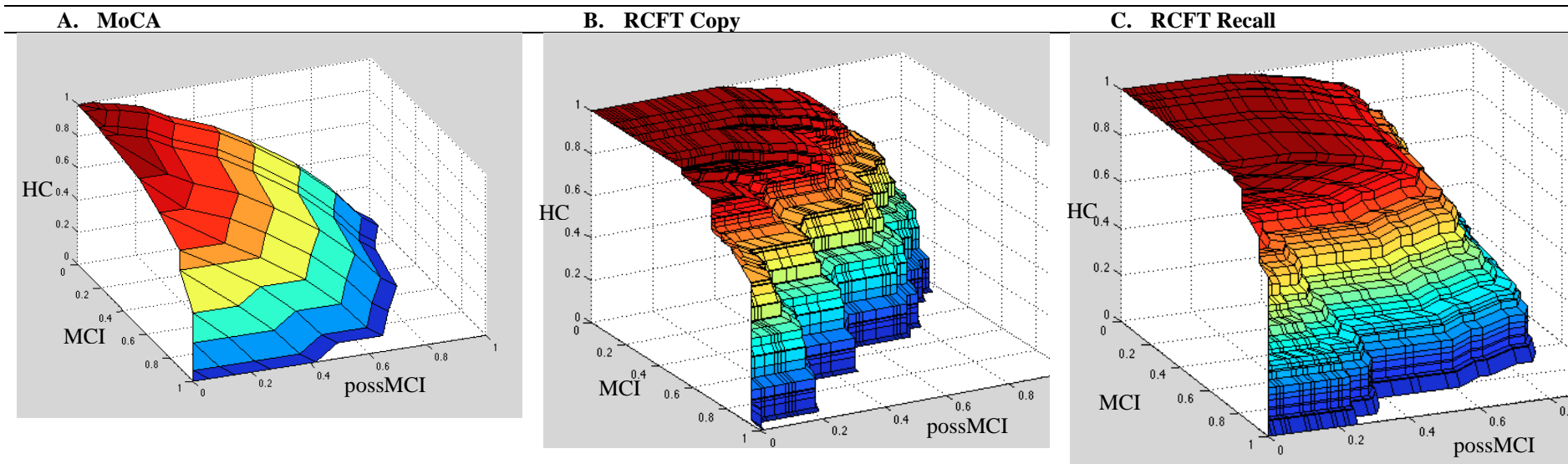


Figure 3-7. Visual representations of the VUS for the MoCA, RCFT Copy and RCFT Recall. Figure courtesy of Associated Professor Christos Nakas. MCI = Confirmed MCI; possMCI = Possible MCI; HC = Probable Healthy Control.

Table 3-7
Results for the Pairwise Comparisons

	Confirmed MCI vs. Possible MCI				Possible MCI vs. Probable HC				Confirmed MCI vs. Probable HC			
	Cut-off	Sensitivity	Specificity	AUC (<i>p</i> -value)	Cut-off	Sensitivity	Specificity	AUC (<i>p</i> -value)	Cut-off	Sensitivity	Specificity	AUC (<i>p</i> -value)
MoCA	<27	0.54	0.88	0.74 (<i>p</i> <0.01)	<27	0.73	0.46	0.63 (<i>p</i> <0.001)	<27	0.73	0.88	0.86 (<i>p</i> <0.001)
RCFT Copy	<-1.49	0.74	0.53	0.61 (<i>p</i> <0.001)	<-0.58	0.90	0.68	0.85 (<i>p</i> <0.001)	<-0.8	0.94	0.71	0.88 (<i>p</i> <0.001)
RCFT Recall	<-1.4	0.82	0.71	0.77 (<i>p</i> <0.01)	<-0.4	0.86	0.67	0.81 (<i>p</i> <0.001)	<-1	0.97	0.82	0.96 (<i>p</i> <0.001)
Combination Model		0.80	0.76	0.82 (<i>p</i> <0.001)		0.88	0.90	0.94 (<i>p</i> <0.001)		0.99	0.94	0.96 (<i>p</i> <0.001)

Note. MCI = Mild Cognitive Impairment; HC = Healthy Control; MoCA = Montreal Cognitive Assessment; RCFT = Rey Complex Figure Test; Combination Model = MoCA + RCFT Copy + RCFT Recall.

3.4 Discussion

The primary purpose of the current study was to determine whether a combination of a brief cognitive screening test (MoCA) along with measures of specific cognitive functions would effectively discriminate between cognitive normal elderly, those with Possible MCI, and those with clearly defined MCI. The current study provided strong evidence that the MoCA and RCFT, particularly its recall trial, produced good discrimination of MCI cases, whereas TMT-A showed relatively poor discrimination. Moreover, the results demonstrated that combining the MoCA with the RCFT Copy and RCFT Recall provided better discrimination of MCI than using single measures. This added benefit of the combination model may be because the RCFT measures a wide range of cognitive abilities including memory, visuospatial and visuoconstruction abilities, as well as more frontal lobe functions, such as planning. In a recent study, Miller et al. (2014) also demonstrated that the addition of the RCFT to the MMSE improved the detection of MCI in the screening process. The MMSE independently correctly classified 88.8% of cognitively normal and 53.4% of MCI, and when supplemented with the RCFT (copy, recall and retention) the percentage increased to 92.5% and 74.1% for cognitively normal and MCI, respectively. Therefore, researchers and clinicians should consider adding the RCFT as an adjunct test to the more routinely used MoCA when screening for cognitive impairment, given that its copy and the immediate recall trial can be completed in less than 10 minutes.

The current study recognised that cognitive decline associated with ageing is a gradual progressive process that exists on a continuum, and that a definable intermediate state may exist between normal cognition and MCI (Duara et al., 2011). Many researchers have referred this state as the Pre-MCI, similar to the Possible MCI in the present study, where individuals do not fully meet formal MCI criteria but they are not 'cognitively normal' either. Duara et al. (2011) examined 275 participants over a 2-3 year period, with annual follow-ups. At baseline, Pre-MCI showed cognitive, functional, motor behavioural and imagining features that were intermediate between normal cognition and MCI states. Over the follow up period, Pre-MCI subjects showed accelerated rates of progression to MCI as compared to cognitively normal subjects, but slower rates of progression to dementia than MCI subjects. Given that Pre-MCI represents an intermediate state between normal cognitive and MCI, it becomes especially valuable to diagnostically separate the three cognitive classes, for tracking progression of cognitive symptoms over time, following up on borderline changes in cognition, and to assess the rate of deterioration in progressive condition. In addition any benefit that can be gained from AD intervention may be most apparent in the earlier stages, thus early detection (i.e., in the MCI or even Pre-MCI stages) is extremely important. The traditional dichotomous ROC approach appears inadequate when one wants to compare and contrast three cognitive classes simultaneously. Hence, the present study employed three-way ROC analysis, which allows concurrent discriminations for the three cognitive classes. Results from the three-way ROC analyses also confirmed a clear benefit of the combination model relative to each individual test. The combination model

not only showed excellent AUC when distinguishing Possible MCI vs. Probable HC, and Confirmed MCI vs. Probable HC, it also provided added diagnostic utility when discriminating Confirmed MCI vs. Possible MCI, concurrently.

A major contribution of the current study is the provision of the cross-tabulation tables containing the cut-off values for each test generated by the combination model (refer to Appendix B, C, and D). Clinicians and other health professional are unlikely to refer to logistic regression equations for clinical decision-making. Hence, cross-tabulation tables have been generated using the logistic regression equation, which enables the examination of the relationships within the range of cut-off points for each test. Unlike previous studies, where a single score is used as the criterion for cut-off, the tables employed by the current study would allow the clinicians to take into account patients score on the MoCA along with their score on the RCFT Copy and RCFT Recall when determining cognitive status. These tables can be simply looked up and are easy to use by health professionals.

There are several limitations to the current study. First, cognitive status was confirmed in relatively few individuals by comprehensive neuropsychological assessment. This small proportion may have caused some classification errors, thus affecting the sensitivity and specificity values generated by ROC analysis. Second, there is a possible circularity effect of using the MoCA, RCFT Copy, RCFT Recall, and TMT-A in both the screening battery and the detailed neuropsychological battery. An ideal

approach to eliminate the circularity effect would be to employ different tests in the detailed neuropsychological battery. However, in addition to the RCFT, we used a number of other tests to define the domain of memory. Therefore, the circularity effect is mitigated by the inclusion of multiple tests in the detailed neuropsychological assessment for each cognitive domain. In any case the proposed combination of scores is relatively independent of the individualised a priori cut-offs used for Probable MCI, Possible MCI and Probable HC. Third, there is by necessity a relative imbalance of sample size between the three cognitive classes, which may have prevented the elucidation of statically significant effects. Larger sample sizes for MCI and Possible MCI may be required for future studies.

3.5 Summary and Conclusion

The current study shows that the MoCA and RCFT demonstrated good discrimination of MCI, and the combination of the two tests showed even better discriminatory power. Given the copy and the immediate recall trial of the RCFT can be completed in less than 10 minutes, researchers and clinicians should consider adding this as an adjunct test to the more routinely used MoCA when screening for cognitive impairment. However, it is important to note the primary purpose of screening is not to provide a diagnosis but to establish the need for an in-depth assessment. Thus, a comprehensive neuropsychological assessment is recommended, particularly given that MCI is a heterogeneous condition and its subtypes may indicate different prognosis, it is necessary to follow up any positive

results with a comprehensive neuropsychological assessment to obtain more information and ascertain specific cognitive weaknesses and strengths of a given individual.

CHAPTER 4 - Non-Pharmacological Interventions in MCI

4.1 Introduction

It is an international priority to develop preventative strategies for AD. One major approach to reduce the prevalence of AD is to develop strategies to delay its onset in those at risk of developing dementia. MCI represents a transitional stage between normal ageing and dementia. This prodromal phase of dementia is recognised as a key period to establish interventions to promote cognitive reserve and counter worsening cognitive symptoms (Albert et al., 2011). The limited efficacy of the current drug therapies in MCI has stimulated growing interest in the use of cognitive intervention for MCI. This chapter reviews the effects of non-pharmacological interventions in the cognitive functions in older people with MCI, but more importantly provides the theoretical basis for the Cognitive Enrichment Programme.

4.2 Non-pharmacological interventions for MCI

In the past few decades, a number of studies have been conducted to examine the potential effects benefits of non-pharmacological interventions in MCI. Chief among these interventions are cognitively based interventions that can be broadly classified as either memory strategy training or multi-domain cognitive training. In addition to

cognitive interventions, physical exercise may also be protective against cognitive decline (Ohman, Savikko, Strandberg, & Pitkala, 2014; Rodakowski, Saghafi, Butters, & Skidmore, 2015; Teixeira et al., 2012). Although the data are limited, physical exercise has been associated with improvements in cognitive function in older adults with MCI. The frequent rationale for physical exercise programs were based on the vascular hypothesis, in that physical activity acts as a protective factor of cognitive decline by reducing the risk of cardiovascular disease often associated with dementia by maintaining healthy blood flow (Orgeta, Regan, & Orrell, 2010). In a recent meta-analytic review of non-pharmacological interventions for MCI, cognitive-based interventions were associated with significant improvements in global cognitive function (effect size = 0.37, 95% CI = 0.07 – 0.68), executive function (effect size = 0.8, 95% CI = 0.09 – 1.5), and delayed memory recall (effect size = 0.31, 95% CI = 0.01 – 0.61), whereas physical exercise was only associated with an improvement in the global cognitive function (effect size = 0.25, 95% CI = 0.08 – 0.41) (Wang et al., 2014). In addition, unlike cognitive activities, physical activities are less likely to directly influence various brain networks, thus only briefly reviewed in the current chapter. Table 4-1 provides an overview of the physical intervention studies in individuals with MCI.

Table 4-1
Physical Exercise in Individuals with MCI

Author (Year)	Format / Components of Intervention	Participants	Study Design	Duration / Frequency	Outcome Measures	Results
Scherder et al. (2005)	Individual Intervention: walking or hand/face exercise	Walking: 15 MCI Hand/face exercises: 13 MCI CG: 15 MCI	RCT	Six 30-min sessions 3/week	Memory, executive function	Between Group Comparisons: a trend of TGs performing better than the CG on tests of executive function, but did not reach significance no beneficial effect on memory processes
van Uffelen et al. (2008)	Group Intervention: TG 1: aerobic walking and vitamin B supplementation TG 2: placebo activity and vitamin B supplementation TG3: aerobic walking and placebo supplementation CG: placebo activity and	TG 1: 71 MCI TG 2: 75 MCI TG 3: 78 MCI CG: 74 MCI	RCT	One hundred and four 60-min sessions 1/week	Memory, global cognitive function, executive function, processing speed, attention	Between Group Comparisons: no improvement in global cognitive function or executive function women with good attendance in aerobic walking improved attention men with good attendance in aerobic walking improved attention
Baker et al. (2010)	Group Intervention: high intensity exercise (treadmill, stationary bicycle, elliptical trainer) or stretching control group	TG: 23 MCI CG: 10 MCI	RCT	Ninety-six 45-60-min sessions 4/week	Memory, processing speed, executive function	Between Group Comparisons: TG improved in executive function, intervention effects were more prominent in female participants.

Varela et al. (2012)	Group Intervention: TG 1: aerobic exercise, cycling, 40% of the heart rate reserve TG 2: aerobic exercise, cycling, 60% of the heart rate reserve CG: recreational activity	TG 1: 17 MCI TG 2: 16 MCI CG: 15 MCI	RCT	Thirty-six 30- min sessions 3/week	Global cognitive function, functional autonomy	Pre-Post Comparisons: no significant intervention effects in either TG groups
Suzuki et al. (2013)	Group Intervention: TG: aerobic exercise, strength training, balance, dual tasking; CG: education about health promotion	TG: 50 MCI CG: 50 MCI	RCT	Forty-eight 90- min sessions 2/week	Memory, global cognitive function, executive function	Between Group Comparisons: TG improved in global cognitive function, immediate memory, and letter fluency
Nagamatsu et al. (2013)	Group Intervention: TG 1: resistance training TG2: aerobic training CG: balance and tone exercises	TG 1: 28 MCI TG 2: 30 MCI CG: 28 MCI	RCT	Fifty-two 60-min sessions 2/week	Memory, reaction time	Between Group Comparisons: TG groups showed greater improvements in reaction times for a spatial memory task when compared to CG

Note. RCT = Randomised Controlled Trial; TG = Treatment Group; CG = Control Group; = MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease.

4.2.1 *Cognitive-Based Interventions*

Given the primacy of memory deficit in most cases of MCI, many of the early cognitive intervention studies concentrated exclusively or largely on the amelioration of memory difficulties (a summary of results from studies of memory training are presented in Table 4-2). These studies focused on teaching memory strategies, using either compensatory and/or restorative type of approaches. Commonly applied compensatory strategies included categorisation, chunking, visual imagery, cueing, elaboration (e.g., Kurz, Pohl, Ramsenthaler, & Sorg, 2009; Londos et al., 2008; S. Rapp, Brenes, & Marsh, 2002). Restorative strategies included spaced retrieval, errorless learning, vanishing cues and reality orientation (e.g., Jean et al., 2010; Troyer, Murphy, Anderson, Moscovitch, & Craik, 2008). While some studies focused on the utility of a particular memory strategy (e.g., Hampstead, Sathian, Moore, Nalisnick, & Stringer, 2008; Jean et al., 2010), most studies applied these techniques simultaneously. Memory strategies are usually delivered in group settings directed by a trainer, over multiple training sessions. These sessions are typically highly structured with segments of the session devoted to teaching the strategies, and practice using the strategies with feedback from the trainer. Besides the memory training component some programmes also offered education about memory, relaxation skills, physical rehabilitation, and life-style education as part of a comprehensive intervention programme (Kurz et al., 2009; Troyer et al., 2008).

More recent cognitive intervention studies have adopted a more global perspective on cognitive functioning. These studies follow the reasonable assumption that cognitive

functions should work together and therefore should be stimulated in concert (a summary of results from multi-domain studies are presented in Table 4-3). Although the memory training component remained as the primary target of these intervention programmes, language, calculation, executive function and construction praxis are also stimulated (Belleville et al., 2006; Buschert et al., 2011; Kinsella et al., 2009; Olazaran et al., 2004; Olchik, Farina, Steibel, Teixeira, & Yassuda, 2013; Tsolaki et al., 2011; Wenisch et al., 2007).

Most of the reviewed studies, whether memory strategy training studies or multi-domain cognitive training studies, reported significant results on measures that were directly related to the aspects targeted during the programme. For example, Hampstead et al. (2008) reported improved reaction time and recognition accuracy on the trained face-name pairs. Similarly, Belleville et al. (2006) demonstrated improvements in the ability to learn face-name pairs following face-name association training. Other authors have described increased memory strategy knowledge (Troyer et al., 2008) and increased compliance with the use of a calendar system after training (Greenaway, Hanna, Lepore, & Smith, 2008). These findings of training-related improvements in MCI demonstrated that elderly with MCI retained the ability to learn new information with repeated exposure, and thus providing support to the view that the brains of people with MCI remain highly plastic.

The ultimate goal of cognitive intervention is, however, to produce transfer of the trained strategies to untrained tasks and to create improvements in the overall level of cognitive functioning. Standardised neuropsychological tests are usually adopted to measure the transfer of the training effects. Overall, multi-domain studies (Table 4-3) showed stronger evidence of transference to standardised neuropsychological tests than studies of pure memory training. For example, Kinsella et al. (2009) provided multi-domain cognitive training to a group of MCI participants, and reported significant changes on a prospective memory task after intervention; another study described improved word list recall following multi-domain cognitive training (Belleville et al., 2006); and a number of studies revealed that MCI participants reached the level of performance of healthy controls after intervention on tests of categorical verbal fluency (Olchik et al., 2013), word-list learning (Olchik et al., 2013), story recall (Olchik et al., 2013), and associative memory (Wenisch et al., 2007). In contrast, only two of the reviewed memory strategy training studies (Table 3-1) reported significant improvement on standardised memory measures (Kurz et al., 2009; S. Rapp et al., 2002). Furthermore, randomised controlled trials of multi-domain cognitive intervention have demonstrated positive effects on global cognitive measures, such as the ADAS-cog (Buschert et al., 2011; Olazaran et al., 2004), the MMSE (Olazaran et al., 2004; Tsolaki et al., 2011), and the MoCA (Tsolaki et al., 2011), and no such effects were reported by studies of memory strategy training. The limited efficacy of memory strategy training is perhaps because it fails to provide broad enriching stimulation for the participants (Gates & Valenzuela, 2010). Hence, suggesting that cognitive intervention aimed to stimulate a range of

cognitive functions is perhaps the more promising method to postpone cognitive decline in persons with MCI.

Table 4-2
Single-Domain Memory Strategy Training in Individuals with MCI

Author (Year)	Format / Components of Intervention	Participants	Study Design	Duration / Frequency	Outcome Measures	Results
Rapp et al. (2002)	Group Intervention: memory strategy training, education, relaxation training, and cognitive restructuring	TG: 9 MCI CG: 10 MCI	RCT	Six 120-min sessions 1/week	Memory, perception of memory impairment, perceived control over memory	Between Group Comparisons: TG showed greater perceived memory ability and control over memory no significant group differences on objective memory measures
Hampstead et al. (2008)	Individual Intervention: memory strategy training (face-name association)	8 MCI	UC	Three 60-min sessions over 2 weeks	Face-name associative memory (trained and untrained)	Pre-Post Comparisons: improved performance on both trained and untrained face-name associations
Greenaway et al. (2008)	Individual Intervention: memory strategy training (training in the use of memory support system, a calendar and organisation system)	20 MCI	UC	Twelve 60-min sessions over 6 weeks	Memory, compliance assessment, activities of daily living, caregiver burden	Pre-Post Comparisons: increased compliance with the memory support system no significant effect on other outcome measures
Londos et al. (2008)	Group Intervention: memory strategy training (compensatory strategies)	15 MCI	UC	Sixteen 150-min sessions over 8 weeks 2/week	Memory, visuospatial skills, attention, processing speed, occupational skills, quality of life	Pre-Post Comparisons: improved in processing speed, occupational skills, and quality of life no significant effect on memory and visuospatial skills

Troyer et al. (2008)	Group Intervention: memory strategy training, relaxation, lifestyle education	TG: 22 MCI CG: 27 MCI	RCT	Ten 120-min session over 6 months	Memory, strategy knowledge and use, memory-related affect and thoughts	Between Group Comparisons: TG showed increased memory strategy knowledge and use no significant group differences on other outcome measures
Kurz et al. (2009)	Group Intervention: memory strategy training, self- assertiveness training, relaxation techniques, stress management and motor exercises	TG: 18 MCI, 10 AD CG: 12 MCI	C	22h/week over 4 weeks	Memory, activities of daily living, mood	Pre-Post Comparisons: TG improved in memory, activities of daily living and mood CG did not show these improvements
Jean et al. (2010)	Group Intervention: errorless or errorful learning for face- name associations	Errorless: 11 MCI Errorful: 11 MCI	RCT	Six 45-min sessions over 3 weeks	Memory, global cognitive function face-name associative memory, subjective memory questionnaire	Between Group Comparisons: both group showed improved capacity to learn face-name associations and were more satisfied with memory functioning no significant effect on other outcome measures
Kinsella et al. (2015)	Group Intervention: Memory strategy training	TG: 53 MCI, 56 HC CG: 53 MCI , 57 HC	RCT	Six weekly sessions	Memory, strategy knowledge, strategy use, wellbeing, self- reported memory ability	Between Group Comparisons: for HC participants improvements were found in memory ability and prospective memory tests for MCI participants gains were found in strategy use only

Note. C = Controlled Study; RCT = Randomised Controlled Trial; UC = Uncontrolled Study; TG = Treatment Group; CG = Control Group; HC = Healthy Control; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease.

Table 4-3
Multi-Domain Cognitive Intervention in Individuals with MCI

Author (Year)	Format / Components of Intervention	Participants	Study Design	Duration / Frequency	Outcome Measures	Results
Olazaran et al. (2004)	Group Intervention: cognitive exercises (memory, attention, language, visuospatial abilities, calculation, and executive function), reality orientation, training of activities of daily living, psychomotor exercises	12 MCI; 48 mild AD; 24 moderate AD TG: 44 CG: 40	RCT	One hundred and three 210-min sessions over 1 year 2/week	Global cognitive functioning, activities of daily living, mood	Between Group Comparisons: TG maintained/improved global cognition and mood CG declined on these measures
Wenisch et al. (2007)	Group Intervention: memory strategy use (categorisation, mental imagery), reality orientation, newspaper review, cognitive exercises (executive function)	12 MCI; 12 HC	UC	Twelve 90-min sessions 1/week	Memory, executive function, mood	MCI vs HC: MCI showed greater improvements on measures of memory than HC
Belleville et al. (2006)	Group Intervention: memory strategy training (interactive imagery, method of loci, face-name association, organisation of text information, verbal organisation-semantic proximity, categorisation, hierarchisation), computer-assisted divided attention and processing speed training	TG: 20 MCI, 9 HC CG: 8 MCI, 8 HC	C	Eight 120-min sessions 1/week	List recall, face-name association, story recall, subjective memory, mood	Pre-Post Comparisons: TG improved in delayed list recall, face-name association, subjective memory and well-being CG did not show these improvements

Kinsella et al. (2009)	Group Intervention: memory strategy training (face-name recall, verbal categorisation and elaboration, visual imagery, errorless learning, spaced retrieval, compensatory strategies), strategies for improving organisational and attentional skills	TG: 22 MCI CG: 25 MCI	RCT	Five 90-min sessions 1/week	Prospective memory, subjective memory, strategies knowledge	Between Group Comparisons: TG improved prospective memory, strategies knowledge no significant differences on subjective memory
Buschert et al. (2011)	Group Intervention: memory strategy training (face-name association, errorless learning, compensatory strategies), reminiscence, psychomotor and recreational tasks, cognitive exercises (memory, attention, and executive function)	TG: 12 MCI, 8 AD CG: 12 MCI, 7 AD	RCT	Twenty 120-min sessions over 6 months	Global cognitive functioning, executive function, memory, mood, activities of daily living	Between Group Comparisons: TG improved global cognition and reduced depressive symptoms no significant effect on other measures
Tsolaki et al. (2011)	Group Intervention: cognitive training in attention, memory and executive function	TG: 104 MCI CG: 72 MCI	RCT	Sixty 270-min sessions over 6 months 1/week	Global cognitive functioning, memory, visuospatial ability, attention, executive function, language	Between Group Comparisons: TG improved global cognition, attention, memory, executive function, visuospatial function, language, daily function CG deteriorated in daily function

Olchik et al. (2013)	Group Intervention: cognitive training in memory, attention and executive function training, plus education or education only	Cognitive training plus education: 16 MCI, 20 HC Education only: 17 MCI, 20 HC CG: 14 MCI, 22 HC	RCT	Eight 90-min sessions 2/week	Executive function and memory	MCI vs HC: MCI showed greater improvements than HC, and were comparable to HC at baseline Between Group Comparisons: cognitive training resulted in higher improvements in executive function and memory measures
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Note. C = Controlled Study; RCT = Randomised Controlled Trial; UC = Uncontrolled Study; TG = Treatment Group; CG = Control Group; HC = Healthy Control; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease.

4.3 Rationale for the Current Study

While multi-domain intervention programmes appeared to demonstrate greater efficacy than memory strategies training, the rationale for many of the programme components in the former programmes was seldom explicitly stated or linked to models in cognitive neuroscience. Some studies have selected techniques or programmes that have demonstrated some efficacy in other memory impaired populations such as traumatic brain injury (TBI). However, neurobiological deficits seen in patients with TBI can be very different from those exhibited by MCI individuals.

The current study proposes an alternative approach to the existing cognitive training programmes. The intent here was to provide MCI individuals a cognitively stimulating environment using a range of complex and novel cognitive activities. There are two lines of evidence to support the utility of cognitive enrichment in this regard. The first draws on the concept of cognitive reserve. The term cognitive reserve describes the brain's resilience to neuropathological damages, it was first introduced to explain why cognitive decline associated with AD is sometimes absent even when significant AD pathology is present (Katzman et al., 1988). The cognitive reserve hypothesis proposes that lifelong experiences, including education, work complexity, and engagement in cognitively stimulating activities result in a greater reserve, which leads to a more efficient use of existing brain networks (Valenzuela, 2008; Valenzuela & Sachdev, 2007).

Hence, individuals with more cognitive reserve would be more successful than someone with less reserve in coping with the same amount of brain pathology.

Studies on cognitive reserve and AD have demonstrated that the risk of dementia remained highly modifiable by experience well into late life (Valenzuela & Sachdev, 2007). Longitudinal studies have also demonstrated that engagement in cognitively stimulating activities during late-life was inversely correlated with the incidence of AD, and this protective effect typically remains even after adjusting for early life experiences and other confounding variables (Fratiglioni, Paillard-Borg, & Winblad, 2004; Scarmeas, Levy, Tang, Manly, & Stern, 2001; Valenzuela, Breakspear, & Sachdev, 2007; R. S. Wilson, Mendes De Leon, et al., 2002). For example, one study measured past and current participation in cognitively stimulating activities of more than 700 elderly participants (R. S. Wilson, Scherr, Schneider, Tang, & Bennett, 2007). Past cognitive activities included items about activities in childhood (ages 6 and 12), young adulthood (age 18), and middle age (age 40). Current activities were those endorsed at study baseline and annually thereafter. The authors first demonstrated that both past and current activities were associated with reduced incidence of MCI and AD, and less rapid decline in cognitive function. However, the effect of past activity attenuated and no longer significant when both past and current activities were examined in a single model suggesting that current activities is a more important predictor of cognitive functions than past activities. Moreover, it appeared that the frequency of participation in late-life activities was also related to the risk of AD. An earlier study reported a dose-dependent

relationship between late-life cognitive activity and the risk of AD, with more frequent participation in cognitive activity associated with a lower risk of AD (Verghese et al., 2003). The risk of AD in a group with moderate level of cognitive activities was 50% lower compared with the low-activity group, whilst those with the highest activity levels had their risk reduced to 33%. Taken together, these results suggest that increasing the cognitive reserve even in elderly persons through cognitively stimulating activities might help to preserve cognitive functioning and delay the onset and progression of AD.

The second line of evidence comes from animal research. While caution must be employed when comparing human and animal models, it is worth considering how successful animal paradigms can better inform the selection of intervention parameters when developing novel intervention programmes for humans. The potential effects of cognitive activity in the prevention or reduction of age-related cognitive decline have been modelled using the environmental enrichment (EE) paradigm in animals. The vast majority of such work to date has been conducted in rodents. EE involves changes to the animals' housing condition which offer enhanced cognitive, motor, sensory and social stimulation in comparison with standard caging (e.g., Nithianantharajah & Hannan, 2006; Will et al., 2004). While different labs have employed different protocols, animals in the EE conditions are generally housed in bigger cages to allow room for exploration and the introduction of a variety of objects. These objects, varying in shape, size, weight, smell and texture, may include tubes, balance platforms, climbing apparatus, balls, or running wheels which are changed on a scheduled basis, often daily, to maintain novelty and

complexity of the animals' environment. Furthermore, EE increases social stimulation through larger number of animals per cage, for example 8 to 12 animals per cage instead of the 3 to 6 per cage in standard housing conditions.

These EE conditions have been found to alter a range of cellular, molecular and behavioural aspects of pathogenesis in animal models including transgenic AD mouse models. At the cellular and molecular level, EE has been associated with decreased amyloid deposition and reduced tauopathy in neurofibrillary tangles (Lahiani-Cohen et al., 2011; Lazarov et al., 2005), greater neurogenesis and improved synaptic neuronal connections (Levi, Jongen-Relo, Feldon, Roses, & Michaelson, 2003), and positive effects on growth factors and neurochemicals that promote brain health (Cracchiolo et al., 2007; Wolf et al., 2006). The positive effects of environmental stimulation extend beyond neurobiology. Behavioural studies have also shown that transgenic mice raised in an enriched environment showed improved performance in various cognitive tasks, including the Morris Water Maze (Costa et al., 2007; Wolf et al., 2006), and the visual novel Object Recognition Test (Polito et al., 2014). In a more recent study, it was found that EE not only demonstrated beneficial effects when applied before disease onset, when it is provided after the disease onset it was also associated with positive effects on amyloid pathology (Herring et al., 2011). In their study, transgenic AD mice were randomly allocated to 60 days of enriched environment either before disease onset (no appearance of A β plaques) or 60 days after the appearance of A β plaques, thus allowing the comparison of the effects of preventative EE (pre-disease-onset) and therapeutic EE

(post-disease-onset). That study found that the preventative EE reduced the number and size of amyloid plaques, which was suggested to reflect an increased degradation and clearance of A β . Therapeutic EE, on the other hand, reduced the growth and fusion of plaque seeds, possibly by inhibiting A β aggregation. Findings from this study provided an experimental basis for application of EE in the prevention and treatment of AD.

The beneficial effects of EE in transgenic animal models of AD clearly illustrated the potential utility of a programme of cognitive, sensory, social stimulation in humans. Although animal EE paradigm cannot be readily translated as an intervention programme for AD patients, it provides the theoretical basis for the development of an analogous intervention programme with the human population. Therefore, aspects of the EE paradigm that are responsible for brain and behavioural changes in animal models provide pointers when developing an analogue for humans. Nithianantharajah and Hannan (2006) concluded that the key feature of EE appears to be the provision of novelty and complexity to the animals' environment, while motor activity potentially adds value to the overall EE effects, but has limited beneficial effect when applied on its own. Studies that compared rodents exposed to wheel running only with rodents exposed to EE have recognised that while enhanced motor activity contributes to some of the beneficial effects, cognitive stimulation is essential to the EE paradigm (Pang, Stam, Nithianantharajah, Howard, & Hannan, 2006; Pawlowicz, Demner, & Lewis, 2010). In addition to cognitive stimulation, social stimulation has also been suggested as an important aspect of the EE paradigm. Renner and Rosenzweig (1986) suggested that

social interaction may have some direct or indirect (e.g. the activity of one animal attracts the attention of another) impact on the effects of EE. Extrapolating from these findings, the key drivers of neural plasticity found in EE studies appears to include the availability of multiple stimuli coupled with novelty in the environment, and opportunity for engagement in social interaction.

There have been some attempts to use a variety of cognitively stimulating tasks in people with MCI, mostly with computerised software programmes. For example, a recent study by Finn and McDonald (2011) used the computerised programme supplied by Lumosity Inc, and gave 30 sessions which each contained four to five cognitive exercises out of six available exercises. All MCI participants began at the same level of difficulty, and once a predetermined criterion of performance was reached for a particular exercise, the level of difficulty was increased. These authors reported improved performance on trained tasks, but little evidence of generalisation of training to the Cambridge Automated Neuropsychological Test Battery (CANTAB; a computerised neuropsychological test battery). Also, non-significant effects were found on self-reported measures of everyday memory function or mood. In contrast, greater efficacy was demonstrated by a study that incorporated social interaction with computer-based cognitive activities. Dannhauser et al. (2014) developed an intervention programme which comprised of three components: physical activity, group-based cognitive stimulation and individual cognitive stimulation. Group-based cognitive activities included activities such as pottery, painting, cooking, tap-dancing, playing brass instruments, rope craft, genealogy, sign language, digital

photography and drawing, whereas individual cognitive stimulation involved computer-based puzzle-type exercises. These authors reported significant treatment effects on several cognitive measures including forward and backwards digit span and category fluency (Dannhauser et al., 2014). It is possible that the limited generalisation reported by Finn and McDonald (2011) may be attributed in part to the fact that their programme did not have any social stimulation. As noted earlier that social interaction has a synergistic effect on the overall EE effect, at least in animal studies (Pawlowicz et al., 2010).

Although computer-based cognitive programmes, especially when incorporated with social interaction, have demonstrated some efficacy in the MCI population, but it is worth noting that aged population often have little familiarity with and sometimes aversion to computers and access to computers is still limited in this age group compared to younger populations (Goodman, Syme, & Eisma, 2003). Their computer use is further impeded by functional deficits such as visual impairments that make reading a computer screen more difficult (Bitterman & Shalev, 2004) and dexterity problems that interfere with typing and moving a computer mouse (Charness & Holley, 2004). Another barrier is financial, as older adults may have limited income to invest in computer equipment, software, and service fees (Fisk & Rogers, 2002). Older adults' sometimes report anxiety about their lack of knowledge (Czaja & Sharit, 1998) and lack of confidence in their ability to master computers (Marquié, Jourdan-Boddaert, & Huet, 2002).

4.4 Functional Brain Networks Relevant to MCI

Cognitive changes in MCI more often reflect pathological changes in the brain rather than psychological variables. Neuroimaging studies have revealed both structural and functional changes in MCI with progressive loss of both grey and white matter, as well as reductions in cerebral metabolism (Dai & He, 2014; De Santi et al., 2001; Misra, Fan, & Davatzikos, 2009; Risacher & Saykin, 2013). Although the medial temporal lobe is thought to be the site of early pathology underlying the initial amnesic syndrome in AD, current theories of AD have posited that neuropathology and functional changes exist in many cortical and subcortical regions in individuals with AD (Andrews-Hanna et al., 2007; Seeley, Crawford, Zhou, Miller, & Greicius, 2009). The discovery of resting state brain networks has suggested that functional communication between anatomically distributed, but functionally linked brain regions is likely to play a key role in complex cognitive processes (van den Heuvel & Hulshoff Pol, 2010). It has been increasingly recognised that cognitive functions are dependent on the integrity of these brain networks, so decline in cognitive abilities is likely to be a result of disruption in multiple networks, rather than alterations in a single brain region (Andrews-Hanna et al., 2007; Brier et al., 2012).

Functional magnetic resonance imaging (fMRI) has allowed the assessment of functional connectivity between spatially distant brain regions by measuring the temporal correlations in the blood-oxygen-level-dependent (BOLD) signal across the brain. In task-related fMRI, MR signal during one cognitive condition (e.g., memory encoding of

novel stimuli) is often compared to a control task (e.g., viewing familiar stimuli) or to a passive baseline fixation (e.g., visual fixation). Comparing the relative changes in the BOLD signal at baseline and during the performance of a task or in response to a stimulus allows one to infer whether certain areas of the brain are activated or deactivated by the task in question. In recent years, there has been an increase in interest in the application of fMRI at rest (i.e., in the absence of an explicit task or stimulus). This technique has been referred to as the resting-state fMRI (RS-fMRI), which measures the spontaneous low frequency fluctuations (<0.1 Hz) in the BOLD signal. Many large-scale resting-state networks have been identified using this technique, and several of these networks are affected in AD and MCI, including the default mode network (DMN), attention network, executive network, and salience network (Agosta et al., 2012). The key nodes in the DMN are the medial prefrontal cortex, posterior cingulate cortex/precuneus, inferior parietal cortex, lateral temporal cortex and, in some descriptions, the hippocampal formation. The attention network includes the lateral prefrontal cortex and temporoparietal regions; the executive network covers several medial and lateral prefrontal cortex areas; and the salience network encompasses the inferior frontal cortex, insula and the anterior cingulate cortex (Agosta et al., 2012; Buckner, Andrews-Hanna, & Schacter, 2008). An interesting feature of the DMN is that, in contrast to the other resting-state networks, regions of the DMN are highly active during an idle state (hence the term default). The DMN is typically deactivated during externally driven cognitive tasks but further activated during internally driven processes, such as mind wandering,

future planning, taking the perspective of the others, navigation, and autobiographical memory (Buckner et al., 2008).

A number of studies have shown that the DMN is particularly vulnerable to the pathological processes seen in AD and is affected even in MCI (Bai et al., 2008; Greicius et al., 2004). Amyloid burden is often considered to be one of the major neuropathological hallmarks of AD. Interestingly, the deposition of the amyloid protein shows a high degree of spatial overlap with areas of the DMN, particularly the posterior regions of the DMN including the precuneus and posterior cingulate cortex (Buckner et al., 2005; Sperling et al., 2009). Furthermore, Adriaanse et al. (2014) found that the amyloid load in the DMN was highest in patients with AD, intermediate in MCI and lowest in controls, suggesting an inverse relationship between amyloid deposits in the DMN and cognitive function in elderly. Studies examining the impact of amyloid pathology on the DMN function have shown that the amount of amyloid accumulation is significantly associated with reduced network connectivity (Drzezga et al., 2011; Hedden et al., 2009; Koch et al., 2014; Mormino et al., 2011; Sheline et al., 2010; Sperling et al., 2009). While it is likely that multiple factors play a role in the decline to AD, these studies suggest that the DMN may play a critical role in the neurodegenerative process of AD.

The most consistent finding of DMN impairment in both MCI and AD is the decreased functional connectivity during resting state, and decreased task-induced

deactivation in the DMN (Hafkemeijer, van der Grond, & Rombouts, 2012). For example, Sorg et al. (2007) compared resting-state DMN connectivity between healthy elderly and MCI, and found that functional connectivity between hippocampus and posterior cingulate cortex was absent in MCI. Others studies have suggested a pattern of decreased functional connectivity from the posterior to anterior portions of the DMN (Bai et al., 2008; Sperling et al., 2010). Furthermore, these alterations were found to be related to the severity of the disease and, therefore, may act as a biomarker of future progression in MCI (Brier et al., 2012; Petrella, Sheldon, Prince, Calhoun, & Doraiswamy, 2011). A recent longitudinal study suggested that functional connectivity between regions comprising the DMN was progressively diminished in MCI and AD, with more severe decreases observed in AD (Petrella et al., 2011). This study also distinguished individuals with MCI who converted to AD from those who remained stable over the 2-3 years, reporting that the converters showed more severe loss of DMN connectivity than the non-converters, which suggested that decreased functional connectivity in the DMN region may be a significant predictor of conversion to AD (Petrella et al., 2011).

Comparing MCI to healthy controls, reduced task-induced deactivation in MCI was found in the posterior cingulate cortex, precuneus, frontal and parietal regions during the performance of cognitively demanding tasks (Hafkemeijer et al., 2012; Rombouts et al., 2005). The DMN task-induced deactivation pattern has also been shown to progressively decrease along the continuum from normal ageing to MCI to AD (Pihlajamaki & Sperling, 2009; Rombouts et al., 2005). Moreover, Celone et al. (2006)

showed that compared to healthy older controls, less impaired MCI had increased task-related deactivation in the medial and lateral parietal regions, whereas more impaired MCI showed decreased deactivation in these regions. This observation of increased task-related deactivation in early MCI provided indications of possible compensatory mechanisms in early MCI. Another interesting finding is that task-induced deactivation is modulated by cognitive reserve in older adults (Bosch et al., 2010), but in an opposite manner for healthy elderly and MCI. In healthy elderly, high cognitive reserve was related to decreased deactivation of the DMN, which has been suggested as a result of more efficient usage of brain networks (Bosch et al., 2010). In contrast, high cognitive reserve in MCI was related to increased activity in brain areas involved in the task and increased deactivation in DMN regions, which indicate possible increased reorganisation of functional compensatory resources in MCI with high cognitive reserve. The finding that pattern of brain activity is modulated by cognitive reserve provided further evidence for the use of cognitive enrichment in MCI.

4.5 The Current Study

The current study examined the effectiveness of a novel cognitive enrichment programme, in individuals with MCI. Unlike any prior programmes, this programme was based on sound theoretical perspectives, as outlined above. It aimed to provide a broad range of cognitive stimulation for elderly with MCI. The cognitive activities included the current programme were therefore very different from the generally non-specific brain

exercises in prior studies. In the current programme, the tasks were designed specifically to influence multiple brain networks identified in fMRI analyses and in particular to focus on changes in the DMN. The novelty of the programme, an idea that was predicated on animal EE research, was maintained by having multiple levels within each of many varying tasks, and unfamiliar features were added at each level, so that performance of the task will remain challenging and not become subject to automation. Moreover, the enrichment programme adopted a dyadic approach which involved the inclusion of a support person (e.g., social support from a spouse or a family member) in the intervention, who becomes instrumental in assisting the person with MCI to carry out the enrichment programme. This dyadic approach has the advantage of promoting social interaction as well as individualise the treatment by tailoring it to a participant's neuropsychological abilities. A rating scale was implemented at the end of each task to permit the user and the research team to evaluate their performance and thus help monitor a 'systematic enrichment plan'. The dyadic approach also offers a possibility of a wide scale dissemination of the programme, as participants are able to complete the enrichment tasks in their own home and pace, with assistance and encouragement from a support person.

The effectiveness of the programme was examined using standardised neuropsychological tests. Functional neuroimaging techniques were also incorporated to measure enrichment-related changes in the DMN. Changes in the patterns of DMN activation or deactivation were measured using standardised fMRI methods, focusing on

increases and decreases in the BOLD signal during experimental conditions compared to the control conditions. Changes in the functional connectivity of the DMN were examined using resting-state fMRI. It was expected that the Cognitive Enrichment Programme would protect further cognitive decline in MCI through its influence on the DMN, as well as other cognitively-based neural networks in the brain.

CHAPTER 5 - The Cognitive Enrichment Programme

5.1 Introduction

The Cognitive Enrichment Programme was developed as a support person based, individualised cognitive intervention designed primarily to influence multiple large-scale functional networks in the brain, especially the default mode network (DMN) in MCI individuals. The goal of the programme was for all MCI participants to engage in network-related cognitive stimulating activities for about 45-60 minutes a day, 3-4 times a week, for four months at the participant's home. This equals or exceeds the frequency of cognitively stimulating activities that have been associated with reduced dementia risk in studies of older population (Verghese et al., 2003; R. S. Wilson, Bennett, et al., 2002). The intervention programme was administered by a support person, especially a significant other such as spouse, but people without a support person had the intervention administered by postgraduate psychology students (including the author).

Given the programme's emphasis on brain networks and specially the DMN, the tasks in the Cognitive Enrichment Programme were different to common non-specific 'brain exercise' activities. They were designed in a specific way to stimulate the DMN or inhibit the DMN through influence on other brain networks. The DMN becomes less

active during engagement in cognitive tasks that demand attention to external stimuli and more active during self-referential cognitive processes (Buckner et al., 2008; Spreng, Mar, & Kim, 2008). Hence, the enrichment tasks were designed so that some tasks would (1) activate the DMN, (2) some deactivate it, while (3) other tasks would require switching between activating and deactivating the DMN. The programme was tailored to each individual's cognitive ability and preference, and individuals worked through the tasks at their own pace, albeit with encouragement and monitoring by the author and other researchers. Participants worked on five to six different tasks at a time, with new tasks introduced periodically; some tasks were given on a more regular basis than others. Importantly, the tasks were designed so most tasks provided multiple difficulty levels, starting with very simple examples and gradually getting more difficult as the person progressed through the programme. In addition, several repeats were included in each level to give participants the opportunity to practice at any given level. The decision when a participant moved on to the next level of a particular task was primarily determined by their rating at the end of each level where they signalled it as 'too easy', 'easy', 'okay', 'hard', or 'too hard'. If a task was rated as 'too easy', 'easy', or 'okay', the participant then moved on to the next level of that task; on the other hand, they repeated the same level if they gave a rating of 'hard' or 'too hard'. On some occasions the support person decided to repeat a particular level, if they considered the participant was having difficulties, even if the participant themselves considered the task as 'okay'. Participants and their support person could request additional repeats if they wanted to have more

attempts at a particular task. Participants were also allowed to skip a level if they were finding them ‘too easy’.

5.2 Tasks Designed to Inhibit Activity in the DMN

Tasks designed to inhibit DMN activities were also referred to as the ‘external’ tasks, as these tasks require attention to external stimuli. The ‘external’ tasks were given to participants from the beginning of the enrichment programme. The order in which participants received these tasks did not differ, but the frequency and speed at which the tasks were given was guided by the participants’ ratings.

5.2.1 *Tangram Puzzle*

The Tangram Puzzle was designed to enhance participants’ ability to visualise and manipulate spatially presented information. Participants were asked to solve puzzles using seven flat puzzle pieces of different shapes and colour (Figure 5-1). The difficulty of the task was modulated by increasing/decreasing the number of missing puzzle pieces. Participants started by completing puzzles with only two pieces missing (Figure 5-1 B) and they gradually move to recreating the whole puzzle using all seven pieces (Figure 5-1 D).

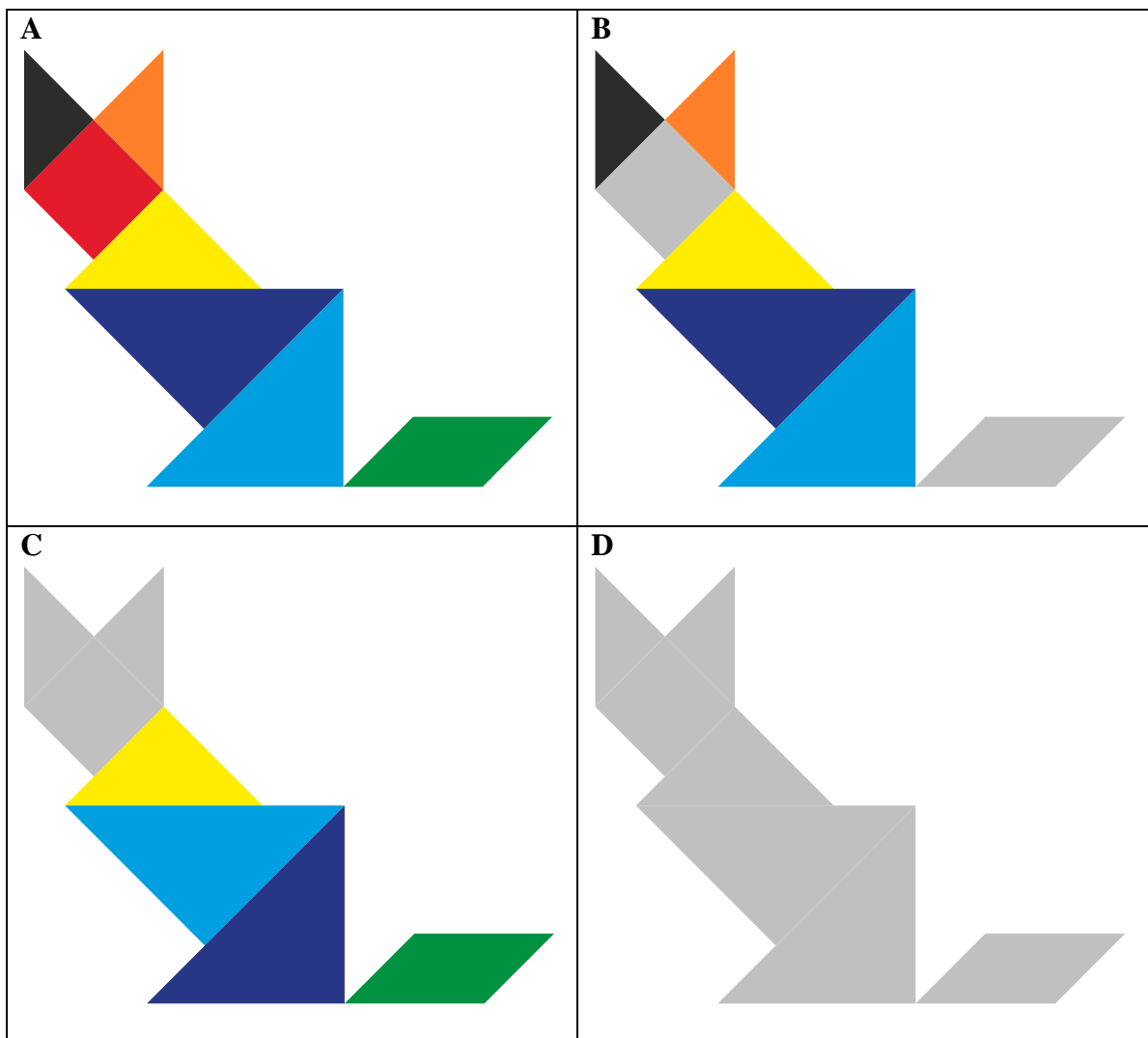


Figure 5-1. Examples of the tangram puzzle task. (A) A completed puzzle. (B) An uncompleted puzzle; participants were asked to fill the two missing pieces. (C) An uncompleted puzzle with three pieces missing. (D) Participants were asked to recreate the puzzle using all seven puzzle pieces.

5.2.2 Numerical Stroop

The ability to inhibit irrelevant information is a crucial part of the attention system.

Individuals with MCI frequently exhibit deficient interference control (Wylie,

Ridderinkhof, Eckerle, & Manning, 2007), so this task was designed to improve their

ability to withstand distraction. The task was adapted from the procedures described by Kaufmann et al. (2006). Their Numerical Stroop task required the participants to compare the magnitude of two simultaneously presented Arabic numerals according to their numerical values (numerical value comparison), or alternatively their physical size (physical size comparison). In the congruent condition the physically larger digit was also numerically larger than the other one. In the incongruent condition the physically larger digit was numerically smaller than the other one. In addition to the congruency effect, two additional levels of interference were included: the distance effect and the physical size effect. The distance effect is achieved through presenting numbers that are either adjacent to each other (e.g., 2 3) or distant number pairs (e.g., 1 9). The physical size difference between digits was manipulated by changing the font size (e.g., 10-point difference vs. 20-point difference). For the numerical comparison, maximal interference was obtained by a small distance effect (i.e., using adjacent pairs), but a large physical size effect (i.e., 20-point difference). Maximal interference for the physical size comparison was obtained by a large distance effect (i.e., using distant pairs), but a small physical size effect (i.e., 10-point difference). Examples of the task stimuli are presented in Figure 5-2.

	Numerical Value Comparison		Physical Size Comparison	
Maximally Incongruent	2	1	9	1
Minimally Incongruent	9	1	2	1

Figure 5-2. Examples of numerical value and physical size comparisons.

5.2.3 *Global-Local*

The Global-Local task was intended to improve participants' processing speed, mental flexibility and visual discrimination abilities. In this task, small (local) letters were arranged to form a single large (global) letter. Initially, participants had to answer whether a given letter is local or global (i.e., is R global or local?; Figure 5-3 A). In the global trials, the instruction was to identify the large letter; for local trials, the instruction was to respond to the small letters. Later on, they had to circle either the global or local letter in response to the cue given (Figure 5-3 B). The difficulty of the task was determined by the frequency that the participant had to switch between the global and local trials. In addition, participants were instructed to switch to an 'internal' task (see

below) when they encountered a shaded stimulus (Figure 5-3 B), and switch back to the Global-Local task after completing the ‘internal’ task.

<p>A</p> <pre> XXXXXXXX X X XXXXXXX X X X X X X X X X X </pre> <p>is R global or local?</p>	<pre> OOOOOOO O O OOOOOOO O O O </pre> <p>is O global or local?</p>	<pre> E E E E E E E E E E E E E E E E E E </pre> <p>is E global or local?</p>	<pre> YYYYYYY Y Y Y Y YYYYYYY </pre> <p>is Y global or local?</p>	<pre> BBBBBB B B B B BBBBBB B B B </pre> <p>is P global or local?</p>	
<p>B</p> <pre> DDDDDD D D D D D DDDDDD </pre> <p>local D C</p>	<pre> T T T T T T T T T T </pre> <p>local T X</p>	<pre> G G G G G G GG G G G G G G G </pre> <p>global G K</p>	<pre> XXXXXXXX X X X X XXXXXXX X X X </pre> <p>local P X</p>	<pre> PPPPPP P P PPPPPP P P PPPPPP </pre> <p>global E P</p>	<pre> YYYYYYY Y Y Y Y YYYYYYY </pre> <p>global Y Z</p>

Figure 5-3. Examples of the global-local task. (A) Participants were asked to decide whether the letter given in the question is local or global. (B) Participants were asked to circle either the global or local letter in response to the stimulus. Shaded stimulus = switch to an ‘internal’ task.

5.2.4 Mental Rotation

The Mental Rotation task was designed to promote participants’ ability to rapidly and accurately rotate a two- or three-dimensional figure. Initially, a variety of two dimensional figures (letters, numbers, everyday objects, and abstract shapes) were used. The difficulty of the task varied on two levels: the familiarity of the figures (from familiar letters, number and symbol, common objects to more abstract shapes), and the degrees of

rotation (50°, 100°, 150°). Participants started on the task by making yes/no decisions (Figure 5-4 A), later on they had to make multi-choice decisions (i.e., selecting the correct answer among distractors; Figure 5-4 B). Three-dimensional pictures were introduced once the participant had mastered the two-dimensional figures. For this part, participants had to decide whether the picture was showing a left or a right hand (Figure 5-4 C). The pictures were taken from a variety of angles, some with part of the hand disguised (i.e., the thumb), which made it more difficult to judge the correct response.

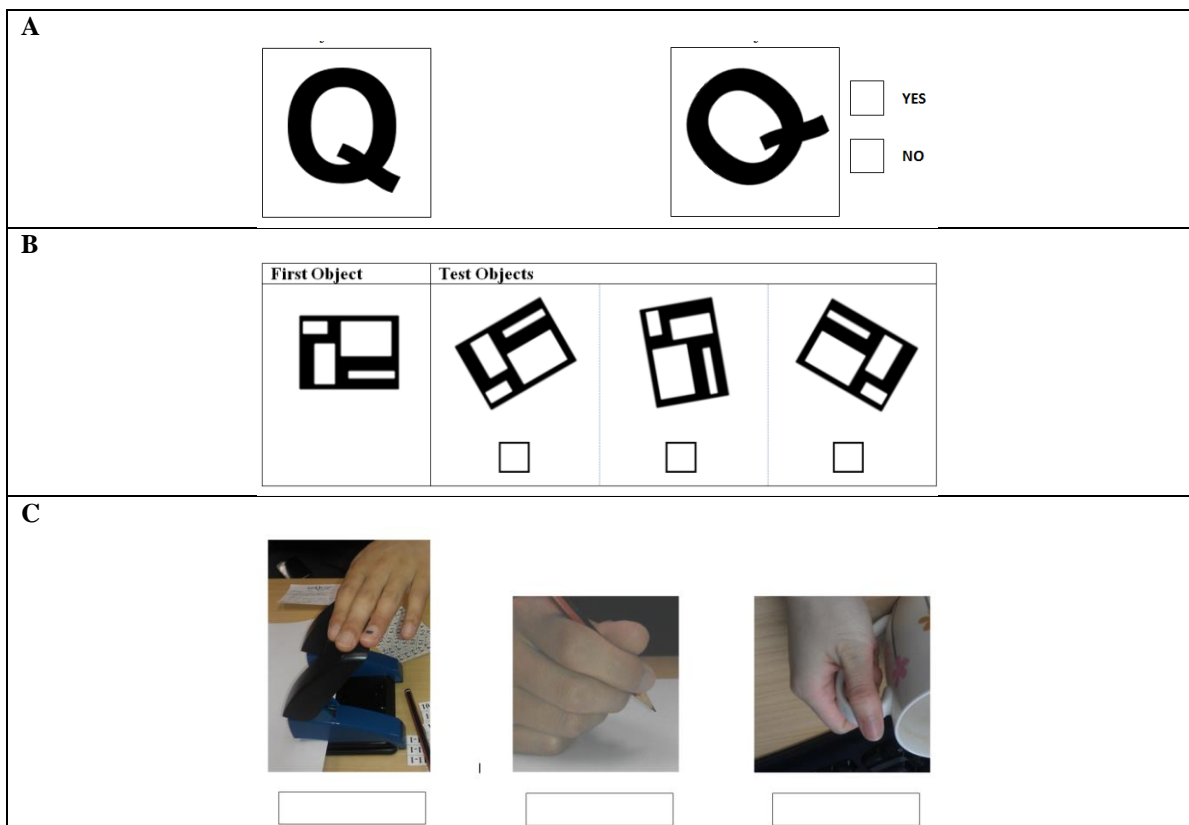


Figure 5-4. Examples of the mental rotation task. (A) An example of the yes/no mental rotation task. (B) An example of the multi-choice mental rotation task. (C) An example of the 3D mental rotation task.

5.2.5 *Bells Test*

This task was adapted from the Bells Test (Gauthier, Dehaut, & Joannette, 1989), which was aimed to enhance attention, speed of processing, and visual searching skills. It required the participant to circle pictures of bells surrounded by various distracters (Figure 5-5). The difficulty of the task was determined by the area that the participant needed to search. Participants started by searching a 8cm x 8cm square and then gradually move to searching a A4 sheet of paper.

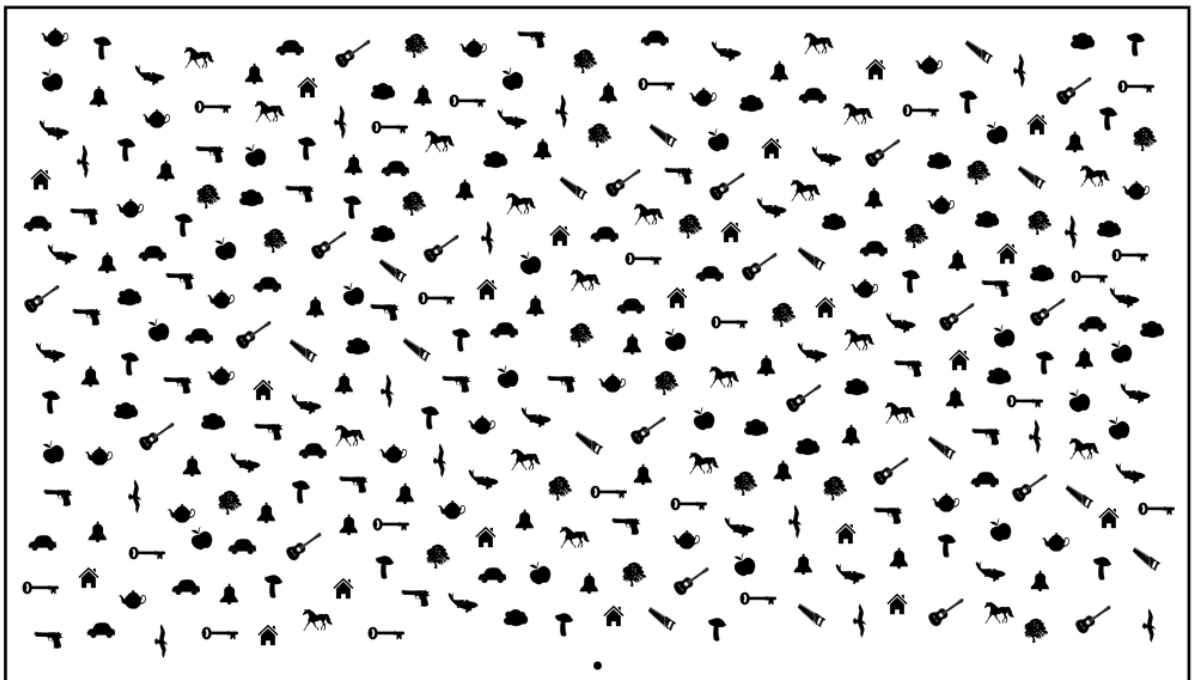


Figure 5-5. An example of the bells test.

5.2.6 Mars Money

Mars Money was designed as a mental arithmetic task

(<https://www.gamesforthebrain.com/game/marsmoney/>). The aim was to improve

participants' attention and working memory by conducting a series of mental calculations

to 'balance' the amount of money held by the two Martians (Figure 5-6). This task varied

in difficulty by the number of notes displayed which presented the wealth of each Martian

(harder levels contained more notes).

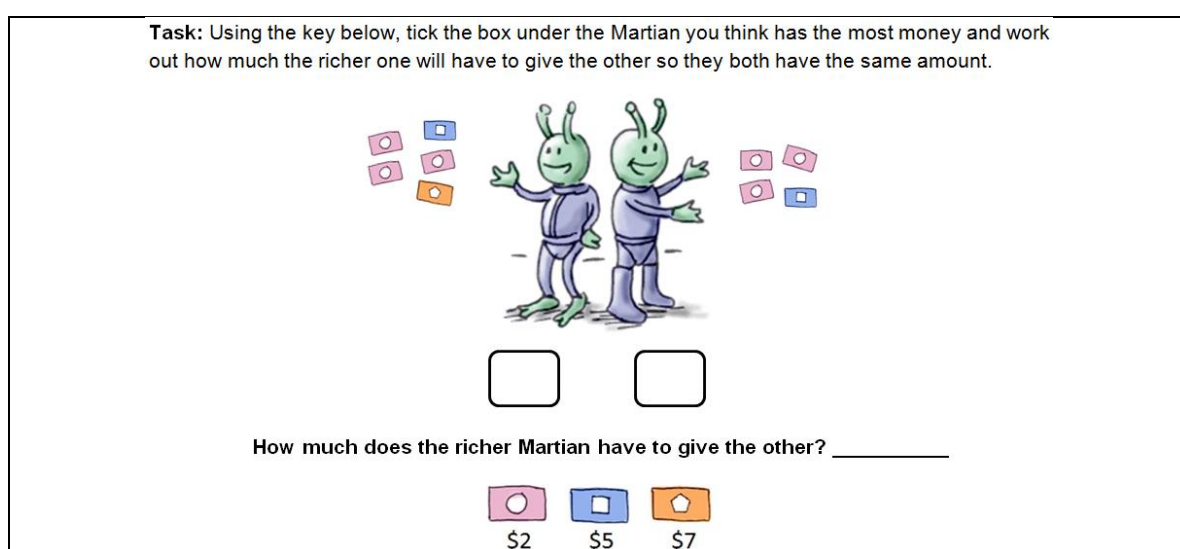


Figure 5-6. An example of mars money.

5.2.7 Mirror Reverse Reading

This task was developed to enhance the participant's ability to process novel information.

Participants were exposed to a perceptual skill learning task requiring them to read

written information in reserved direction. This task varied in difficulty by introducing the

text in various fonts, some of which were more difficult to read than others, along with the length of material being read. Participants began with single words (Figure 5-7 A) and continued to sentences through to whole passages (Figure 5-7 B). Questions directly related to the written material were asked periodically to facilitate understanding.

<p>A</p> <p style="text-align: center;"> DOG HORSE GREEN CAMEL MONKEY </p>	<p>B</p> <p style="text-align: center;"> I wandered lonely as a cloud That floats on high o'er vales and hills, When all at once I saw a crowd, A host, of golden daffodils; Beside the lake, beneath the trees, Fluttering and dancing in the breeze. </p>
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Figure 5-7. Examples of mirror reverse reading. (A) Mirrored reserved words. (B) Mirror reserved paragraph.

5.2.8 *Rearranging Muddled Pictures*

Rearranging Muddled Pictures was designed to improve participants' sequencing and planning skills by sorting muddled scenes of events into their temporal order. In this task, participants were shown muddled photo sequences of an activity (e.g., making a cup of coffee; Figure 5-8) and asked to mentally arrange these photos into their chronological order. The difficulty of this task was adjusted by the number of available photo sequences.

CHAPTER 5 - The Cognitive Enrichment Programme

Making a Cup of Coffee

Task: Mentally rearrange these photos into their correct order and tick (in the box) which photo would appear **2nd** in the sequence.




☐☐☐

Figure 5-8. An example of rearranging muddled pictures.

5.2.9 Toy Store

This task was designed to improve performance in associative memory by requiring participants to remember names of toys associated with specific children. Participants were first introduced to the children and required to learn their names, followed by their associated toys (Figure 5-9). The difficulty of this task was varied by the number of children and the toys associated with each.











<p><small>Participant: Remember the names of these children</small></p> <div style="text-align: center;"><p>My name is Gerald Morris</p><p>My name is James Stewart</p><p>My name is Melissa Russell</p></div>	<p><small>Participant: What are their names? Write this in the space below</small></p> <div style="text-align: center;"></div> <p>.....</p> <p><small>Participant: You will now be shown which toys these two like. Be sure to look at them carefully and try to remember them.</small></p> <div style="display: flex; justify-content: space-around;"><div><p>I like these toys</p><p>I like these toys</p></div><div><p>I like these toys</p></div></div>	<p><small>Participant: Match up the toys with the correct child.</small></p> <div style="text-align: center;"></div> <div style="display: flex; justify-content: space-around; margin-top: 20px;"> </div>
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Figure 5-9. An example of toy store.

5.2.10 Split Words

This task was aimed to promote working memory and attention. In this task, words have been cut in half and rearranged, with the first half the words in the first column and second half in the second column. Participants were required to match up the split words to create whole words. The difficulty of the task varied from matching the split words in two columns (Figure 5-10 A), then to three columns in the original order of the word (Figure 5-10 B), then to matching the fragments appearing in any column and not necessarily in the same as the order the original words (Figure 5-10 C).

A

Participant: Using a pencil, draw a line joining the first two letters of the split words below to the last two letters in the opposite column to make up the three four-letter words.

BE	ME
TI	TY
CI	ST

B

Participant: Using a pencil, match up these triple split word pairs to create names of African animals. The first one has been done for you.

che	ck	ah
ja	et	fe
ba	pha	on

C

Participant: Using a pencil, connect these jumbled split word pairs to create words. The first one has been done for you.

ble	ath
att	bre
jum	ack

Figure 5-10. Examples of split words. (A) Word fragments organised in two columns. (B) Word fragments organised in three columns. (C) Word fragments appearing not necessarily in the same order as the original word.

5.2.11 *Word Shapes*

Word Shapes were designed as a word recognition task to improve attention and visuospatial function in participants. Each word is corresponded with a unique shape (sometimes called the Bouma shape), which matched the outline of the specific word. Tall letters (e.g., h, l) were represented with tall boxes; and shorter letters (e.g., s, o) had shorter boxes; while letters that overhang below (e.g., p, g) had boxes which hang lower. Participants were required to match each of these unique shapes with the corresponding word from a list (Figure 5-11).

Match each of these words with their unique shapes below:	
sought eaten scent baker complete	
Write your answers on the lines below:	
□□□□□	_____
□□□□□	_____
□□□□□	_____
□□□□□	_____
□□□□□	_____

Figure 5-11. An example of word shapes.

5.2.12 *Tricky Tiles*

The aim of this task was to improve visuospatial memory by exercising participants' ability to memorise the location of coloured squares in a grid. Following the

memorisation trial, participants were required to reproduce the pattern they had just seen by placing the coloured squares in their correct location. The difficulty of this task was varied by using different grid sizes and the number of colours presented in the patterns (Figure 5-12). More difficult trials had a greater number of squares in the grid, along with varying colours (Figure 5-12 B).

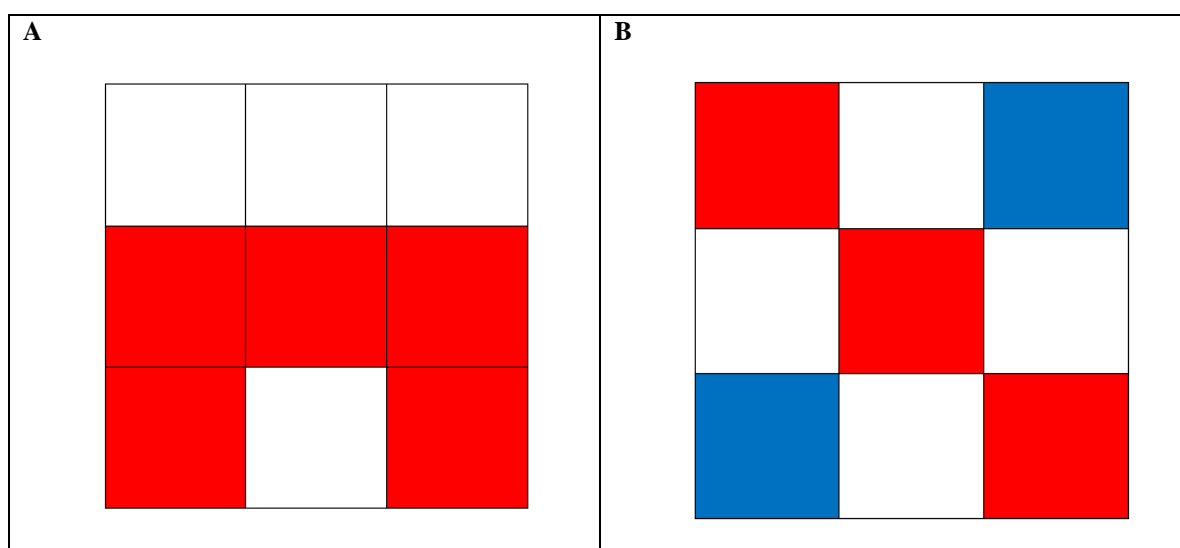


Figure 5-12. Examples of tricky tiles. (A) Pattern made of tiles of the same colour. (B) Pattern made of tiles of two different colours.

5.2.13 Card Game

The Card Game was intended to facilitate mental flexibility, inhibition and speed of processing. To encourage inhibition participants flicked through a set of playing cards and responded yes or no to each card based on a predetermined rule, but upon seeing an ace participants had to change to a new rule. As the person progressed through the task,

not only the rules got more complex (e.g., same suit as previous card; one value higher or lower to previous), they also had to make more frequent switches between the rules.

5.2.14 Self-Selected Pointing

In Self-Selected Pointing task, participants were presented with a series of pages with an array of objects. Objects on each page were always the same but arranged in different configurations on different pages. Participants were asked to self-select one object to point to on the first page, and then pick a new object every new page and keep track of they have pointed to previously. The difficulty of the task increased as the number of objects increased from 3 to 4 then eventually to 12 objects. In addition, the objects also went from more concrete common objects (Figure 5-13 A) to more abstract items (Figure 5-13 B).

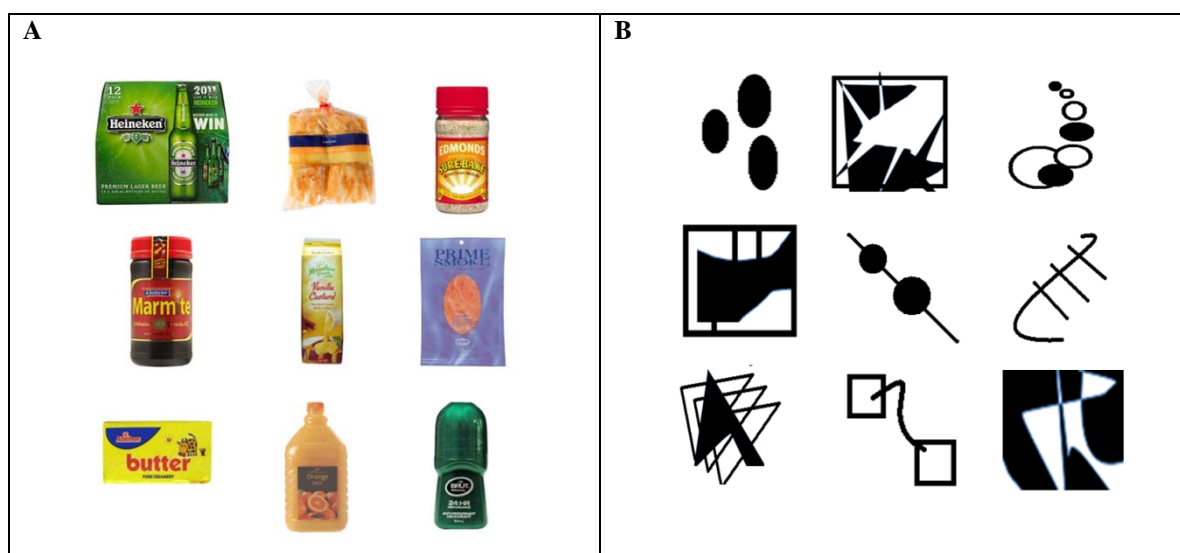


Figure 5-13. Examples of self-selected pointing. (A) Concrete common objects. (B) Abstract items.

5.3 Tasks Designed to Elicit DMN Activity

Accumulating evidence has suggested that several internally directed cognitive processes, including remembering the past, envisioning the future, conceiving the view-point of others, and spatial navigation are associated with increased activity in DMN (Buckner et al., 2008; Buckner & Carroll, 2007; Dixon, Fox, & Christoff, 2014; Spreng et al., 2008). Tasks were developed for this enrichment programme based on these cognitive processes to elicit DMN activity. These tasks were referred to as ‘internal’ tasks due to the involvement of internally directed attention to thoughts, memories and mental imagery. The ‘internal’ tasks were introduced approximately 6-7 weeks after starting the enrichment programme. These tasks were delivered to the participants in a separate folder to the ‘external’ tasks, and participants were instructed to alternate between the ‘external’ and ‘internal’ tasks whilst completing the tasks.

5.3.1 *Hebb-Williams Maze*

This task was adapted from the Hebb-Williams Maze task (Meunier, Saint-Marc, & Destrade, 1986), and involved participants forming a mental imagery of a maze and navigating their way through it. Participants were gently blindfolded and were instructed to trace with a pen through a wooden maze from the start (positioned in the bottom right corner) to finish (positioned in the top left corner) onto a sheet underneath the maze. Mazes were always given in pairs, participants traced through each maze five times. After tracing through the pair of mazes, participants were instructed to draw free hand on a

blank piece of paper their mental representation of their path through the first maze only from start to finish. Participants were not able to view the maze before blindfolding, and remained blindfolded for the duration of the task.

5.3.2 *Autobiographical Memory*


Autobiographical memory is referred to as the episodic recollection of personal events from one's own life (Rubin, Schrauf, & Greenberg, 2003). During autobiographical recall, individuals must project themselves back in time to re-experience the event, and this is often accompanied with by a feeling of reminiscence (Rubin, 2005). Unlike the other tasks where the support person assists the MCI participant in completing the task, this task was carried out by a research assistant. During the initial session, the researcher selected a memory from the Autobiographical Memory Interview (AMI; Kopelman, Wilson, & Baddeley, 1989), and prompted the participant to share that memory in as much detail as possible, by reflecting on it through mental time travel. The AMI was administered at the start of the enrichment programme and involved participants recalling nine episodic events across their lifespan (refer to Grenfell, 2013 for more details). In approximately fortnightly visits by the research assistant, participants repeated the procedure with the memory recalled in the previous session and with a different memory recalled on the AMI. During these sessions the researcher used a 'quilting' strategy to encourage the participants to elicit increasingly detailed recall of each memory. Quilting refers technique that has been developed to help patients with dementia to put pieces of

their personal narratives together by asking more questions or repeating an important phrase or sentence in the person's narrative to elicit additional information of the event (Moore & Davis, 2002).

5.3.3 *Moral Decision Making*

Moral decision making involves the evaluation of actions that concern norms and values established in a social environment (Ciaramelli, Muccioli, Ladavas, & di Pellegrino, 2007; Prehn et al., 2008). In order to judge another person's behaviour as morally right or wrong, one must try to infer that person's intentions and predict the possible outcomes if those intentions are acted upon (Knobe, 2005; Moll, de Oliveira-Souza, Bramati, & Grafman, 2002). In this task, participants were given a scenario and were forced to choose between two different hypothetical statements about how they could react if they were a person in the scenario (Figure 5-14).

Mr Jones has a good friend who tells Mr Jones that he has committed a terrible crime. At first Mr Jones promises not to tell anyone, but he soon finds out that an innocent man has been sent to jail for this crime. He asks his friend to confess. His friend refuses.



Moral Decision - If you were Mr Jones, what would you do?

Choose either **INFORM** or **KEEP QUIET**

Non-moral Decision – If you were the innocent man, how would you be feeling?

Choose either **CALM** or **UPSET**

Figure 5-14. An example of the moral decision making task.

5.3.4 *Faux Pas*

Faux pas is a French term, which refers to a socially awkward or tactless act. In this task, participants were given brief written scenarios of social situations (Gregory et al., 2002; Stone, Baron-Cohen, & Knight, 1998), and they were asked to identify whether a character unintentionally said something hurtful to another character, committing what is called a 'faux pas'. An example of a social faux pas is illustrated in Figure 5-15.

Recognising a faux pas requires both an understanding of false or mistaken belief and an empathic inference of the effect it has on someone, and such cognitive processes are related to increased DMN activity (Buckner & Carroll, 2007). If a social faux pas had been identified in the scenario participants had to say what the faux pas was and who committed it and how they thought that person felt. To check understanding of the story participants answered two control questions that related to events explicitly stated in the scenario. If no faux pas was identified participants did not answer what the faux pas was, who committed it and how they thought that person felt, instead skipping to the control questions.

A - a social faux pas

Jill had just moved into a new flat. Jill went shopping and bought some new curtains for her bedroom. When she had just finished decorating the flat, her best friend, Lisa, came over. Jill gave her a tour of the flat and asked, "How do you like my bedroom?" "Those curtains are horrible," Lisa said. "I hope you're going to get some new ones!"

B - not a social faux pas

Vicky was at a party at her friend Oliver's house. She was talking to Oliver when another woman came up to them. She was one of Oliver's neighbours. The woman said, "Hello," then turned to Vicky and said, "I don't think we've met. I'm Maria, what's your name?" "I'm Vicky." "Would anyone like something to drink?" Oliver asked.

Figure 5-15. Examples of social faux pas.

5.3.5 *Reading the Mind in the Eye*

The Reading the Mind in the Eye test (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997) was developed to measure ‘Theory of Mind’ or the ability to recognise and understand another person’s mental state. This test was adapted for the current study, which required the participant to judge an emotion based on pictures of sets of eyes. Participants began with choosing between two contrasting emotions (Figure 5-16 A) for each set of eyes, progressing to choosing between four emotions (Figure 5-16 B) that were similar in nature. Participants were instructed to pick the emotion they thought was most accurate depiction of ‘the mind in the eyes’.



Figure 5-16. Examples of the reading the mind in the eye. (A) Choosing between two contrasting emotions. (B) Choosing between four emotions similar in nature.

5.3.6 *Envisioning the Future*

Prospection or thinking about the future has been linked with an increased activation in the DMN (Buckner & Carroll, 2007). In this task, participants were given scenarios and instructed to plan their actions in response to these scenarios. Each scenario included both a written description and pictures to prompt possible responses (Figure 5-17). Participants were instructed to give descriptions as detailed as possible, to visualise the future events and situations, and to not limit those descriptions to the picture prompts.

The rare butterfly tiger

A new species of animal has recently been discovered; the butterfly tiger, which is a tiger with butterfly wings. This animal has never yet been photographed or filmed.

There is a prize of 1 million dollars for the first person to obtain a photo or film footage of this animal. The last place this animal was spotted was on Borneo Desert Island.

Your task: Give a description of how you would go about capturing this animal on camera.

It is important that you imagine and then visualise in your mind to help expand your description.







Figure 5-17. An example of the envisioning the future task.

CHAPTER 6 - Cognitive Enrichment Outcomes: task-related and neuropsychological findings

6.1 Introduction

This chapter provides an overview of the study design and the feasibility and efficacy of the Cognitive Enrichment Programme. Enrichment task-related changes and findings on standardised neuropsychological measures are reported and discussed in this chapter. Functional MRI (fMRI) procedures and results are reported in the following chapter (Chapter 7).

6.2 Method

Following detailed neuropsychological assessment (described in Chapter 3), 18 MCI participants were identified (17 through cognitive screening plus an additional MCI referred through a local neurologist). Each MCI participant completed pre- and post-enrichment assessments, which included standardised neuropsychological tests (Figure 6-1) and MRI scanning (refer to Chapter 7). For comparison purposes, 11 age and education matched healthy controls were also identified, classification criteria included: (1) intact functioning on memory tests (i.e., no memory scores below -1.5SD); (2) preserved general cognition (i.e., MoCA > 26, DRS-2 scaled score > 9); and (3) normal activities of daily living (i.e., a total CDR score of 0). Healthy control participants completed pre-

enrichment assessments only. Table 6-1 provides the demographic and cognitive characteristics of the MCI participants and healthy controls at baseline (t1).

6.2.1 *Neuropsychological Assessment Procedure*

In addition to the detailed neuropsychological assessment administered at the baseline of the study (t1; described in Chapter 4), a briefer assessment was conducted immediately prior to the start (t2) of the Cognitive Enrichment Programme, which consisted of a subset of tests from the full battery of tests used at baseline (Table 6-2). The primary aim of the detailed neuropsychological assessment (t1) was to determine the individual's cognitive status, and to facilitate the selection of individuals into the enrichment programme. In contrast, the briefer neuropsychological evaluation was conducted at a time much closer to the start of enrichment (87 days prior to the start of enrichment), and thus provided an estimation of each individual's cognitive functioning at that point. Post-enrichment neuropsychological evaluation was administered, on average, 18 days after the completion of the enrichment tasks or the waitlist period. Full battery of cognitive tests was given at the end (t3). Table 6-2 details the cognitive tests used at each time point.

CHAPTER 6 - Task-Related and Neuropsychological Results

Table 6-1

Baseline Demographic and Cognitive Characteristics of MCI and Healthy Controls; Mean (SD)

	MCI (n = 13)	Healthy control (n = 11)	t-score
Demographic Variables			
Age (years)	75.9 (4.72)	75.9 (3.51)	0.01
Education (years)	12.8 (2.82)	12.6 (2.58)	0.19
Gender (Male : Female)	9 : 4	6 : 5	
Premorbid IQ	113.4 (11.91)	118.2 (8.02)	-1.13
CDR	0.35 (0.24)		
General Cognitive functions			
MoCA ***	21.8 (2.58)	27.1 (1.76)	-5.71
DRS-2 (scaled score) ***	9.4 (2.29)	13.3 (1.95)	-4.42
ADAS-Cog 11 (raw score) ***	10.1 (2.46)	3.4 (2.02)	7.18
Executive Function			
Trail Making Test-Part B	0.58 (0.85)	0.98 (0.51)	-1.38
Action Fluency *	-0.26 (1.01)	0.59 (0.54)	-2.49
Verbal Fluency	0.36 (1.23)	0.49 (1.35)	-0.24
Category Fluency	0.97 (1.20)	1.79 (0.82)	-1.91
Category Switching	0.08 (1.37)	0.94 (0.83)	-1.82
Stroop Interference	0.15 (1.57)	0.91 (0.37)	-1.56
Design Fluency Filled Dots	0.51 (0.92)	0.55 (0.83)	-0.09
Design Fluency Empty Dots	0.67 (0.94)	0.39 (0.65)	0.81
Design Fluency Switching	0.38 (1.35)	1.12 (0.79)	-1.59
Attention and Processing Speed			
Trail Making Test-Part A	0.71 (0.62)	1.15 (0.41)	-2.01
Digit Span	0.46 (1.21)	0.97 (0.61)	-1.26
SDMT Written ***	-0.54 (0.85)	1.09 (1.00)	-4.32
SDMT Oral ***	-0.69 (0.69)	0.91 (0.83)	-5.15
Stroop Colour Naming	-0.00 (0.96)	0.39 (0.51)	-1.22
Stroop Word Naming	0.15 (0.98)	0.55 (0.49)	-1.22
Learning and Memory			
BVMT-R Total Recall ***	-2.02 (0.61)	0.35 (1.00)	-7.11
BVMT-R Delayed Recall ***	-1.91 (0.81)	0.59 (0.82)	-7.49
Story Recall Immediate Recall *	5.31 (3.38)	8.50 (1.83)	-2.80
Story Recall Delayed Recall **	3.69 (2.55)	6.91 (1.88)	-3.45
CVLT-II SF Total Recall ***	-0.15 (0.96)	1.99 (0.42)	-6.85
CVLT-II SF Short Delay ***	-0.77 (1.28)	2.09 (1.09)	-5.81
CVLT-II SF Long Delay ***	-0.50 (0.89)	1.36 (0.84)	-5.25
RCFT Immediate Recall ***	-1.48 (0.79)	1.91 (0.69)	-11.14
RCFT Delayed Recall ***	-1.35 (1.03)	1.73 (1.02)	-7.32
RI-48 Immediate Recall (raw score) **	37.2 (6.92)	45.1 (3.14)	-3.47
RI-48 Delayed Recall (raw score) ***	17.5 (6.29)	29.0 (4.75)	-4.99
Visual Association Test ***	-1.06 (0.97)	-0.07 (0.24)	-3.28
Visuospatial Function			
Matrix Reasoning	0.18 (0.85)	0.97 (1.09)	-2.00
RCFT copy ***	-1.36 (0.99)	0.30 (0.35)	-5.32
Silhouettes (percentile)	30.2 (31.54)	50.6 (28.85)	-1.64
Judgement Of Line Orientation *	0.29 (0.71)	0.82 (0.46)	-2.09
Language			
Boston Naming	0.01 (1.05)	0.40 (0.69)	-1.05
Token Test	-0.36 (0.68)	-0.12 (0.39)	-1.02

Note. Neuropsychological test values are z scores based on age- and education-adjusted norms, unless otherwise stated. SDMT = Symbol Digit Modalities Test; BVMT-R = Brief visuospatial Memory Test-Revised; MoCA = Montreal Cognitive Assessment; DRS-2 = Dementia Rating Scale-2; ADAS-Cog = Alzheimer's Disease Assessment Scale-cognitive subscale; CVLT-II SF = California Verbal Learning Test-II Short Form; RCFT = Rey Complex Figure Test; RI-48 = Rappel Indice 48 items.

* $p < 0.05$. ** $p < 0.01$. *** $p < 0.00$.

6.2.2 *MRI Procedure*

Refer to Chapter 7.

6.2.3 *Random Allocation*

MCI participants were randomly allocated to either the intervention group or the waitlist group (Figure 6-1). Block randomisation was used to achieve balance in the allocation of participants. A block size of two was chosen. Each test was assigned with a specific weighting, tests of memory functions and general cognitive abilities received higher weightings than tests of other cognitive functions. The overall weighted score represents the degree of cognitive impairment (higher score = more impaired; lower score = less impaired). MCI participants were rank ordered based on the severity of their cognitive impairment. The random allocation sequence (1 = intervention; 0 = waitlist) was generated by Random Allocation Software version 1.0.0 (<http://random-allocation-software.software.informer.com>). To achieve matched groups, the randomisation procedure was repeated until the two groups matched on age, education and cognitive performance.

CHAPTER 6 - Task-Related and Neuropsychological Results

Table 6-2

Neuropsychological Tests Administered at Three Different Time Points

Tests	Baseline (t1)	Start (t2)	End (t3)
MoCA	√		√
DRS-2	√		√
ADAS-Cog	√		√
Trail Making Test	√		√
Letter Fluency	√	√	√
Category Fluency	√	√	√
Category Switching	√	√	√
Action Fluency	√		√
Stroop Interference	√	√	√
Design Fluency	√	√	√
SDMT	√	√	√
Digit Span	√		√
CVLT-II SF	√		√
BVMT-R	√	√	√
RCFT	√		√
Story Recall	√	√	√
RI-48	√		√
Visual Association Test	√		√
Matrix Reasoning	√		√
Silhouettes	√		√
Judgment Of Line Orientation	√		√
Boston Naming	√		√
Token Test	√		√

Note. MoCA = Montreal Cognitive Assessment; DRS-2 = Dementia Rating Scale-2; ADAS-Cog = Alzheimer's Disease Assessment Scale-cognitive subscale; SDMT = Symbol Digit Modality Test; CVLT-II SF = California Verbal Learning Test-II Short Form; BVMT-R = Brief Visuospatial Memory Test-Revised; RCFT = Rey Complex Figure Test; RI-48 = Rappel Indice 48 Items.

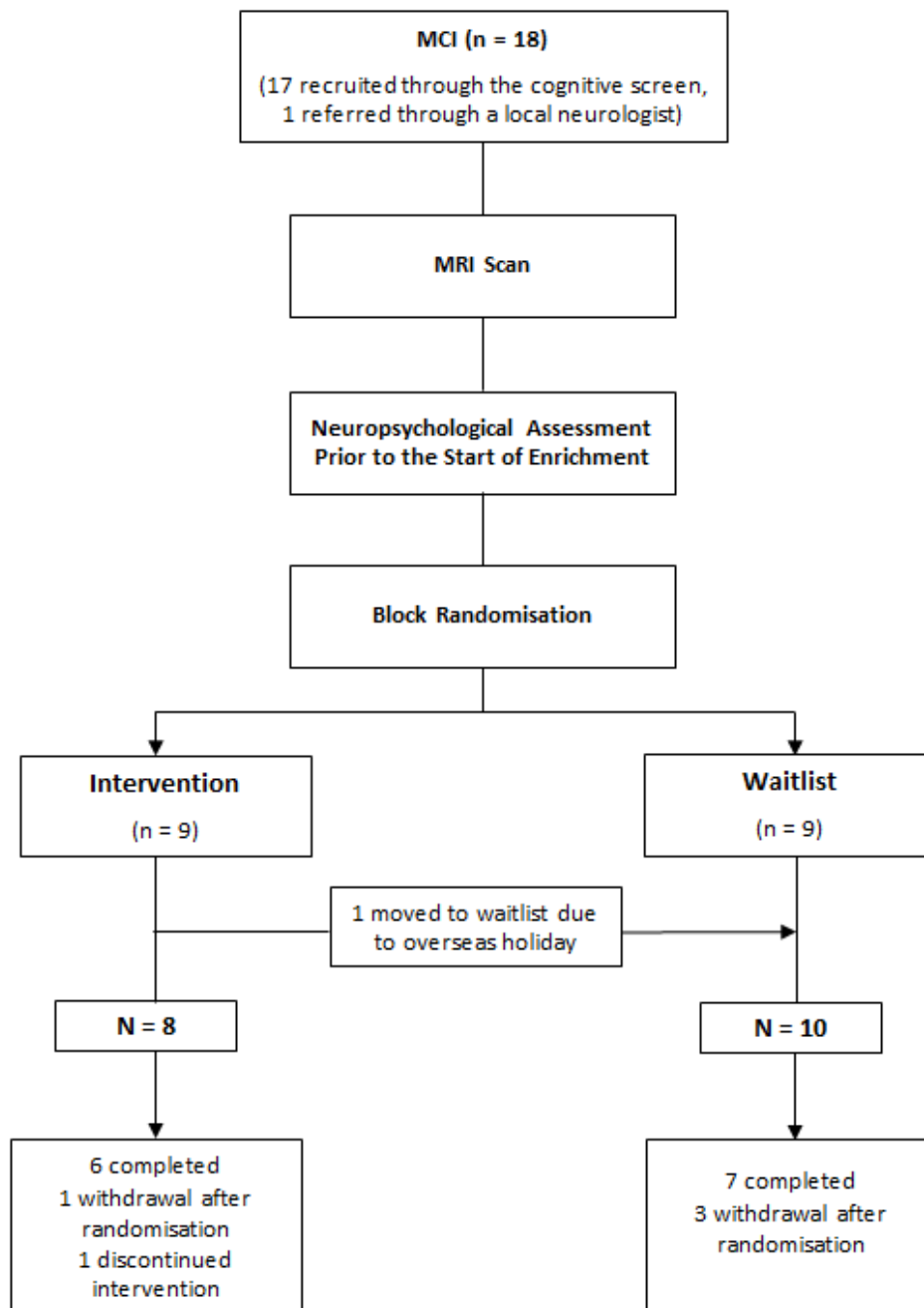


Figure 6-1. Participant flow diagram from randomisation through to study completion. A total of 18 MCI (17 Confirmed MCI as mentioned in Chapter 4 plus an addition MCI referred through a local neurologist) were randomised into the intervention and waitlist group. One intervention participant had to be moved to the waitlist group due to overseas holiday. One intervention participant (increased family commitment) and three waitlist participants (discomfort with cognitive testing; lacking motivation) withdrew before beginning the intervention, but after randomisation. One intervention participant discontinued within the first week of cognitive enrichment due to increased work commitments.

6.2.4 *Statistical Analyses*

The question of interest was whether the decline in scores from pre-intervention (t1 or t2) to post-intervention (t3) is greater for the waitlist group than it is for the enriched group. A series of analyses of covariance (ANCOVA) were conducted, with the difference score between pre- and post-intervention (i.e., primary measures: t2 minus t3; secondary measures: t1 minus t3) as the dependent variable, and the pre-test as the covariate. That is, this model assessed the differences in the pre-post means after accounting for pre-intervention values. Unless otherwise noted, statistical effects associated with $p < 0.05$ were reported as significant, and effects with $p < 0.20$ were reported as indicative on an exploratory basis and given the likelihood of type II errors with this sample size (Stallard, 2012). Data were analysed using Statistica 12 (www.statsoft.com). Cohen's d , expressing the effect size of comparisons, was calculated to gain a better understanding of the range of intervention related benefits. The effect sizes and their 95% confidence intervals were calculated using the difference score (post minus pre), but did not account for the individual's pre-test performance. The effect size for the intervention effect estimates the magnitude of the effect present in the population, expressed in standardised units. In case of a null hypothesis (no effect), a zero effect size is expected. The null hypothesis is rejected, when the confidence interval of the effect size does not span zero. Effect sizes of 0.2, 0.5 and 0.8 are considered as small, medium, and large, respectively. Effect sizes were calculated using Power and Precision (www.poweranalysis.com).

6.3 Results

6.3.1 *Participants vs. Drop-Outs*

To determine the representativeness of the participant sample, comparisons were made between individuals who completed the study and those who dropped out of the programme. The results showed no group differences in sex, age, years of education or cognitive scores, with the exception of Design Fluency Empty Dots. The score was significantly lower in the drop-out group ($M = -0.53$, $SD = 0.76$) than in the participant group ($M = 0.67$, $SD = 0.94$; $t = -2.53$, $p < 0.05$). Overall, the two groups were comparable with respects to preclinical stages of AD. On the a priori basis of compliance of at least three months continuance in the study, drop-outs were excluded from further statistical analyses.

6.3.2 *Intervention vs. Waitlist Participants*

Demographic and clinical variables of the intervention and waitlist participants are presented in Table 6-3. Intervention participants were slightly older and had more years of education than the waitlist group, but none of the variables listed in Table 6-3 showed significant differences. Baseline (t1) performances on neuropsychological tests are presented in Table 6-4. At baseline, comparable performances were observed between the two groups, with the exception of TMT-B ($t = -2.64$, $p < 0.05$) and Stroop Colour Naming ($t = -2.22$, $p < 0.05$), the waitlist controls obtained higher scores than the intervention group on both tests.

Similarly, comparable performances on the neuropsychological tests were observed between the two groups at the start of the Cognitive Enrichment Programme (t2). Table 6-5 provides the cognitive characteristics of the two groups at the start of the cognitive enrichment programme (t2).

Table 6-3
Baseline Demographic Characteristics of Intervention and Waitlist Groups; Mean (SD)

	Intervention (n = 6)	Waitlist (n = 7)
Age (years)	78 (3.01)	74 (5.59)
Education (years)	14 (2.88)	12 (2.33)
Gender (Male : Female)	4 : 2	5 : 2
Premorbid IQ	114 (8.44)	113 (14.96)
CDR	0.33 (0.29)	0.30 (0.27)

Note. CDR = Clinical Dementia Rating.

6.3.3 *Feasibility and Acceptance of the Cognitive Enrichment Programme*

The randomised controlled trial (RCT) was conducted from August 2013 to February 2014. Due to individual variability, the length of the intervention programme ranged from four months to six months. One participant progressed through the enrichment tasks at a much slower pace than the others; in order for him to be exposed to a good variety of tasks his programme was extended to approximately six months. All intervention participants and their caregiver were able to use the programme independently and successfully after initial instruction from the research team. Of the people that started the programme, 83% completed the intervention, with one participant discontinuing after the first week of cognitive enrichment, due to lack of time and work commitment, not

because of difficulty using the programme. No adverse events were reported from either group.

6.3.4 *Performance on Cognitive Enrichment Tasks*

It is postulated that an effective Cognitive Enrichment Programme must provide varied cognitive activities that require continuous effort by the participants. Thus, the difficulty of the enrichment tasks was manipulated, so that each task contained multiple levels that would continue to challenge participants' abilities. Furthermore, rating scales were implemented at the end of each level to avoid distress in participants and at the same time to provide continual cognitive challenges (i.e., if they rated the task as 'too difficult' they can repeat that level again, but if they rated as 'too easy' then they can skip a level).

Tangram Puzzle and Mirror Reverse Reading provided good illustrations of how the tasks were manipulated and participants' progression through the tasks (Figure 6-2 and 6-3). For Tangram Puzzle, as the number of missing puzzle pieces increased from two to seven (Figure 6-2 A), participants rated the task as more difficult (Figure 6-2 D) and required more repeats before progressing onto the next level (Figure 6-2 B). However, participants were still able to maintain a high level of performance, between 85% - 100% of correct responses (Figure 6-2 C), despite the increased mental load, which suggested an improvement in their cognitive abilities during the intervention. The

percentage of correct responses was calculated as the average over the total number of attempts.

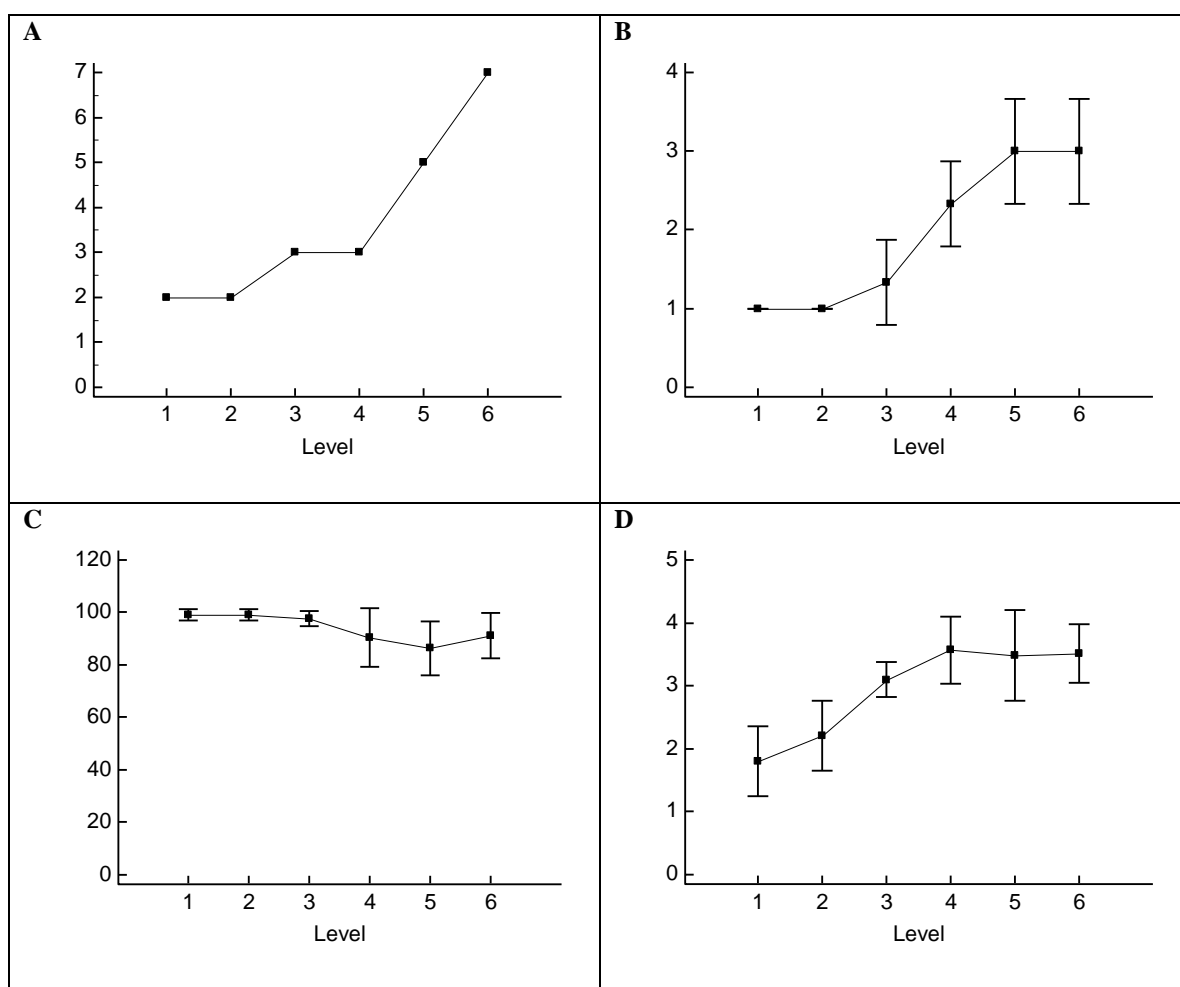


Figure 6-2. Tangram puzzle performance. Example of manipulated parameters and performances during enrichment (A), number of attempts (B), percentage of correct responses (C), and difficulty rating (D). Error bars represent 95% confidence intervals.

Another example of task-related improvements was illustrated by Mirror Reverse Reading (Figure 6-3). There were no data available on the accuracy of performance, as it was an orally administered task involving participants reading mirror reversed text.

Nonetheless, participants rated the task as more difficult (Figure 6-3 B) as they progressed through the task and required more attempts at the same level before feeling confident to move onto the next level (Figure 6-3 A). The drop in the number of attempts at level six was due to participants reaching the end of the enrichment programme, and not having a chance to repeat that particular level despite finding it more difficult than previous levels.

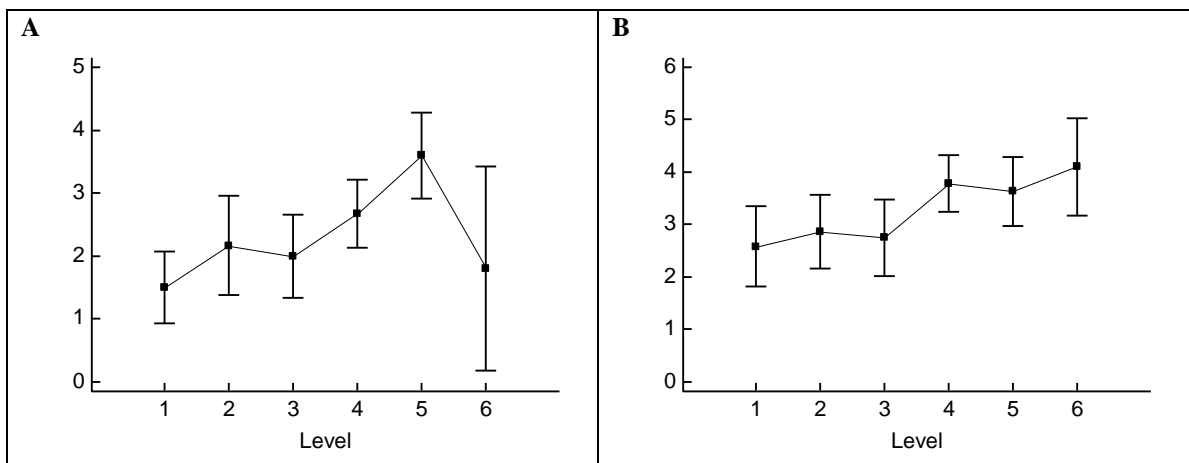


Figure 6-3. Mirror reverse reading performance. Number of attempts (A), and difficulty rating (B). Error bars represent 95% confidence intervals.

6.3.5 Performance on Standardised Neuropsychological Tests

Primary outcome measures consisted of tests that were administered at both the start (t2) and the end (t3) of the enrichment programme (Table 6-4). A significant group difference was observed for BVMT-R Delayed Recall, [$F(1, 10) = 4.97, p < 0.05, d = 0.63$], with a greater decline observed in the waitlist group. In addition, the group difference for BVMT-R Total Recall [$F(1, 10) = 2.74, p = 0.13, d = 0.76$] and Stroop Interference [F

(1, 10) = 3.09, $p = 0.11$, $d = 0.73$] approached significance in favour of the intervention group. Medium to large effect sizes were also observed for Verbal Fluency [$F(1, 10) = 0.32$, $p = 0.59$, $d = 0.58$] and SDMT [$F(1, 10) = 1.38$, $p = 0.27$, $d = 0.81$].

Secondary outcome measures consisted of additional tests that were only administered at baseline (t1) and at the end of enrichment (t4). Although none of these measures reached statistical significance (Table 6-5), medium effects were observed on tests of general cognitive function (e.g., MoCA [$F(1, 10) = 0.48$, $p = 0.50$, $d = 0.50$]; DRS-2 [$F(1, 10) = 0.78$, $p = 0.40$, $d = 0.60$]). Additionally, CVLT-II SF Short Delayed Recall approached statistical significance in favour of the intervention group [$F(1, 10) = 2.72$, $p = 0.13$, $d = 0.80$]. On tests measuring visuospatial abilities, a large effect size was observed for RCFT Copy [$F(1, 10) = 3.33$, $p = 0.10$, $d = 1.10$]. Furthermore, a medium to large effect size was found for Digit Span [$F(1, 10) = 0.01$, $p = 0.95$, $d = 0.56$], Boston Naming [$F(1, 10) = 1.43$, $p = 0.26$, $d = 0.71$], and TMT-B [$F(1, 10) = 0.01$, $p = 0.97$, $d = 0.81$].

Table 6-4

Performance on Primary Outcome Measures at Pre- and Post-Intervention

	Pre-Intervention		Post-Intervention		Difference Score		<i>p</i> -value	Effect Size (95% CI) [#]
	Intervention (<i>n</i> = 6)	Waitlist (<i>n</i> = 7)	Intervention (<i>n</i> = 6)	Waitlist (<i>n</i> = 7)	Intervention (<i>n</i> = 6)	Waitlist (<i>n</i> = 7)		
Executive Function								
Verbal Fluency	-0.11 (1.62)	0.76 (1.24)	0.67 (1.81)	0.95 (0.73)	0.78 (0.72)	0.19 (1.20)	NS	0.58 (-0.60 – 1.77)
Category Fluency	-0.06 (1.51)	0.19 (0.92)	1.00 (1.44)	1.29 (1.18)	1.06 (0.44)	1.10 (1.10)	NS	-0.05 (-1.23 – 1.14)
Category Switching	-0.11 (1.56)	-0.14 (1.15)	-0.06 (1.90)	-0.19 (1.34)	0.06 (0.39)	-0.05 (1.32)	NS	0.11 (-1.08 – 1.30)
Stroop Interference	-0.22 (1.34)	0.81 (0.57)	0.06 (1.67)	0.76 (0.69)	0.28 (0.58)	-0.05 (0.30)	0.11	0.73 (-0.45 – 1.92)
Design Fluency Filled Dots	0.67 (0.99)	0.38 (1.48)	1.00 (1.27)	0.48 (0.96)	0.33 (0.76)	0.10 (0.86)	NS	0.28 (-0.91 – 1.47)
Design Fluency Empty Dots	0.39 (1.12)	0.33 (1.31)	0.67 (1.37)	0.67 (0.88)	0.28 (0.44)	0.33 (1.06)	NS	-0.06 (-1.25 – 1.13)
Design Fluency Switching	0.22 (1.66)	-0.29 (1.52)	0.67 (1.49)	0.29 (1.03)	0.45 (0.66)	0.57 (0.69)	NS	-0.18 (-1.36 – 1.01)
Attention and Processing Speed								
SDMT	-0.83 (0.75)	-0.29 (0.57)	-0.50 (0.77)	-0.43 (0.89)	0.33 (0.52)	-0.14 (0.63)	NS	0.81 (-0.38 – 1.99)
Stroop Colour Naming	-0.06 (1.02)	0.52 (0.33)	-0.11 (1.29)	0.43 (0.76)	-0.06 (0.75)	-0.10 (0.54)	NS	0.06 (-1.13 – 1.25)
Stroop Word Naming	0.22 (0.66)	0.52 (0.69)	0.28 (1.10)	0.57 (0.71)	0.05 (0.77)	0.05 (0.36)	NS	0.00 (-1.19 – 1.19)
Learning and Memory								
BVMT-R Total Recall	-1.52 (1.15)	-1.34 (1.13)	-1.53 (0.96)	-1.99 (0.56)	-0.02 (0.66)	-0.64 (0.93)	0.13	0.76 (-0.43 – 1.94)
BVMT-R Delayed Recall	-1.33 (1.36)	-1.20 (1.28)	-1.53 (0.82)	-1.90 (0.54)	-0.20 (0.70)	-0.70 (0.86)	0.05	0.63 (-0.56 – 1.82)
Story Immediate Recall	-0.22 (1.60)	-0.38 (0.70)	0.00 (1.96)	-0.43 (1.12)	0.22 (0.65)	-0.05 (1.25)	NS	0.26 (-0.92 – 1.45)
Story Delayed Recall	-0.06 (1.22)	-0.67 (0.67)	0.00 (1.05)	-0.81 (0.98)	0.06 (0.54)	-0.14 (0.86)	NS	0.27 (-0.91 – 1.46)

Note. Neuropsychological test values are *z* scores based on age- and education-adjusted norms. SDMT = Symbol Digit Modalities Test; BVMT-R = Brief Visuospatial Memory Test-Revised.

[#] Effect sizes were calculated based on the difference score, and did not take into account of pre-intervention performance.

Table 6-5

Performance on Secondary Outcome Measures at Baseline and Post-Intervention

	Baseline		Post-Intervention		Difference Score		<i>p</i> -value	Effect size (95% CI) [#]
	Intervention (<i>n</i> = 6)	Waitlist (<i>n</i> = 7)	Intervention (<i>n</i> = 6)	Waitlist (<i>n</i> = 7)	Intervention (<i>n</i> = 6)	Waitlist (<i>n</i> = 7)		
General Cognitive Function								
MoCA (raw)	21(3.46)	23 (1.40)	23 (4.22)	23 (3.68)	1.83 (3.87)	0.14 (2.85)	NS	0.50 (-0.68 – 1.69)
DRS-2 (scale)	9 (2.45)	10 (2.29)	10 (4.18)	9 (2.31)	1.33 (2.42)	-0.71 (4.07)	NS	0.60 (-0.59 – 1.78)
ADAS-Cog 11 (raw)	10 (3.20)	11 (1.72)	11 (7.12)	12 (4.01)	-1.33 (5.15)	-1.62 (2.85)	NS	0.07 (-1.12 – 1.26)
Executive Function								
TMT-B	0.03 (0.92)	1.05 (0.43)	0.49 (0.59)	1.02 (0.62)	0.46 (0.73)	-0.03 (0.48)	NS	0.81 (-0.38 – 2.00)
Action Fluency	-0.25 (1.41)	-0.26 (0.64)	0.22 (0.78)	0.29 (0.64)	0.47 (1.34)	0.55 (0.40)	NS	-0.08 (-1.27 – 1.10)
Attention and Processing Speed								
TMT-A	0.56 (0.66)	0.85 (0.60)	0.45 (0.75)	1.00 (0.85)	-0.11 (0.42)	0.16 (0.45)	NS	-0.62 (-1.81 – 0.57)
Digit Span	-0.11 (1.22)	0.95 (1.05)	0.11 (1.00)	0.81 (0.77)	0.22 (0.72)	-0.14 (0.57)	NS	0.56 (-0.63 – 1.75)
Learning and Memory								
CVLT-II SF Total Recall	-0.28 (1.14)	-0.03 (0.84)	0.17 (1.55)	0.36 (0.83)	0.45 (0.95)	0.39 (0.47)	NS	0.08 (-1.10 – 1.27)
CVLT-II SF Short Delay	-0.75 (1.81)	-0.79 (0.76)	0.50 (1.41)	-0.50 (1.08)	1.25 (1.44)	0.29 (0.95)	0.13	0.80 (-0.39 – 1.99)
CVLT-II SF Long Delay	-0.42 (1.11)	-0.57 (0.73)	0.00 (1.05)	-0.57 (0.84)	0.42 (1.16)	0.00 (0.71)	NS	0.45 (-0.74 – 1.63)
RCFT Immediate Recall	-1.38 (0.78)	-1.57 (0.84)	-0.50 (1.28)	-1.11 (1.19)	0.88 (1.17)	0.46 (1.14)	NS	0.36 (-0.82 – 1.55)
RCFT Delayed Recall	-1.42 (0.73)	-1.30 (1.29)	-0.97 (1.45)	-1.00 (1.17)	0.45 (1.39)	0.30 (1.31)	NS	0.11 (-1.08 – 1.30)
RI-48 Immediate Recall	39.33 (8.50)	35.43 (5.22)	38.00 (9.53)	35.14 (5.27)	-1.33 (2.34)	-0.29 (2.69)	NS	-0.41 (-1.60 – 0.78)
RI-48 Delayed Recall	19.67 (7.15)	15.57 (5.26)	19.00 (10.71)	15.14 (6.89)	-0.67 (4.80)	-0.43 (4.12)	NS	-0.05 (-1.24 – 1.13)
Visual Association Test	-1.13 (1.05)	-1.00 (0.98)	-1.17 (1.11)	-1.20 (1.07)	-0.03 (0.37)	-0.20 (0.61)	NS	0.33 (-0.86 – 1.52)
Visuospatial Function								
Matrix Reasoning	0.33 (1.01)	0.05 (0.73)	0.50 (1.07)	-0.14 (1.20)	0.17 (1.21)	-0.19 (0.61)	NS	0.39 (-0.80 – 1.57)
RCFT Copy	-1.29 (1.18)	-1.42 (0.88)	-0.86 (1.16)	-1.68 (1.06)	0.43 (0.90)	-0.26 (0.43)	0.10	1.10 (-0.18 – 2.19)
Silhouettes (percentile)	29.95 (33.77)	30.37(32.23)	40.88 (38.24)	35.27 (35.70)	10.93 (33.15)	4.90 (22.58)	NS	0.22 (-0.97 – 1.40)
JLO	0.31 (0.65)	0.29 (0.81)	0.22 (0.85)	0.29 (0.64)	-0.08 (0.49)	0.00 (0.41)	NS	-0.18 (-1.73 – 1.01)

Language

Boston naming	-0.11 (1.19)	0.11 (1.01)	-0.25 (0.97)	-0.66 (1.55)	-0.15 (0.82)	-0.76 (0.89)	NS	0.71 (-0.48 – 1.90)
Token test	-0.56 (0.86)	-0.19 (0.49)	-0.22 (0.53)	0.00 (0.00)	0.34 (0.67)	0.19 (0.49)	NS	0.26 (-0.93 – 1.45)

Note. Neuropsychological test values are Z scores (except where specified) based on age- and education-adjusted norms. MoCA = Montreal Cognitive Assessment; DRS-2 = Dementia Rating Scale-2; ADAS-Cog = Alzheimer's Disease Assessment Scale-cognitive subscale; TMT = Trail Making Test; CVLT-II SF = California Verbal Learning Test-II Short Form; RCFT = Rey Complex Figure Test; RI-48 = Rappel Indice 48 items; JLO = Judgement of Line Orientation.

[#] Effect sizes were calculated based on the difference score, and did not take into account of pre-intervention performance.

6.4 Discussion

The goal of this chapter was to assess the feasibility and efficacy of the Cognitive Enrichment Programme in persons with MCI. Participants of the programme were faced with cognitively stimulating tasks that called upon a range of cognitive functions.

6.4.1 *Feasibility of the Cognitive Enrichment Programme*

One important aspect of a successful cognitive intervention programme is whether it is able to retain participants' interest and motivation to such a degree that extensive amounts of the tasks can be completed. Completion rates are one way to evaluate these issues. The current study achieved a high level of participation in both intervention and waitlist participants. The attrition rate was relatively low in spite the fact that the programme was relatively demanding and involved a substantial time commitment (45-60 min/d, 3-4 d/wk for at least 4 months), not only for the participants but also for their caregivers. The involvement of a caregiver could be an important factor in the high completion rate; the dyadic interaction between MCI participants and their support people is likely to have facilitated participants' motivation and effort. Most previous cognitive intervention programmes were professional-led, but we found that a support person based programme is also possible and well-accepted by individuals with MCI and their families. This finding is consistent with a study by Margrett and Willis (2006), which showed that older adults could successfully implement a cognitive training programme at home without a formal trainer. Hence, suggests that support person based cognitive intervention

may be a valuable alternative to group formats. Support person based cognitive intervention also offers the advantage of tailoring the programme to each individual's need.

6.4.2 *Enrichment Task-Related Improvements*

In the present study, the enrichment tasks were designed in a fashion so that the tasks tailored each participant's cognition, but at the same time provided continual challenges and offered variety. Although no formal testing was conducted on the enrichment tasks, task-related improvements can be inferred using a number of measures. Firstly, the parameters of the tasks were manipulated to produce increments in difficulty at each level, and the increments were adjusted according to the subjective rating of the participant. Therefore, advancing to the next level usually indicated that the person had shown improved performance on the previous level with repeated exposure. Furthermore, improvements can be measured through the percentage of correct responses at each level. Although this information is not always available for all the tasks and is dependent on the accurate recording of such information by the support person, nonetheless it provides valuable information on a person's progression on the enrichment tasks. It was found in the present study that even with increased cognitive load, participants were still able to achieve a high level of accuracy on the tasks. It is important to note that a stabilised performance should be interpreted as an improvement in performance since the complexity of the enrichment tasks was gradually increased. These results are thus in line

with previous findings of improvements on measures that are directly related to the trained tasks (Belleville et al., 2006; Greenaway et al., 2008; Hampstead et al., 2008; Jean et al., 2010; Troyer et al., 2008).

6.4.3 *Beneficial Effects on General Cognitive Status*

The Cognitive Enrichment Programme produced a medium effect size for two of the global cognitive measures, namely the MoCA and DRS-2. Although these effects did not reach statistical significance, but they were in the expected direction, and their sizes suggest that a larger trial may be warranted. Previous studies using multi-domain cognitive intervention have reported significant intervention effect on global cognitive measures such the ADAS-cog (Buschert et al., 2011) and MMSE (Buschert et al., 2011; Olazaran et al., 2004). We also included the ADAS-cog as a measure of global cognitive status. However, we failed to find a significant intervention effect on the ADAS-cog. Taken together, our results combined with results from previous studies indicated that cognitive intervention involving multi-domain stimulation has the potential to induce generalised cognitive benefits.

6.4.4 *Beneficial Effects on Memory*

It was found that the Cognitive Enrichment Programme had a significant beneficial effect on the BVMT-R Delayed Recall. This beneficial effect of long-term retrieval of visual information was shown by a greater decline of the BVMT-R Delayed Recall in the

waitlist participants, suggesting cognitive enrichment may protect against further memory decline in MCI individuals. In contrast, no significant differences were found on the RCFT Immediate Recall and Delayed Recall, which are also measures of visuospatial memory. Although both intervention and waitlist group showed improved recall of the complex figure, greater improvements were observed in the intervention group than the waitlist group. The lack of significance may be partly attributed to a practice effect. While alternate forms were used at each occasion for the BVMT-R, the same RCFT complex figure was administered at each point, which presents a problem in the evaluation of memory when participants are asked to memorise the same information on more than one occasion. A number of our participants reported that they remembered seeing the complex figure on repeated examinations. It is possible that following the initial exposure, the RCFT has lost its novelty thereby inflating the recall test score. Examination on a related measure (RCFT Copy) revealed that intervention participants' ability to copy the complex figure was greatly improved, while the waitlist group declined. This effect approached significance and resulted in a large effect size. Sullivan, Mathalon, Ha, Zipursky, and Pfefferbaum (1992) argued that the copy score not only provides information about drawing accuracy of the complex figure, it also reflects planning and organisation abilities, which may also influence stimulus encoding and retrieval processes involved in the subsequent recall trials. A different study examined the effects of different types of encoding strategies reported that organised copying strategies resulted in better recall performance of the visual design than disorganised strategies (Newman & Krikorian, 2001). Furthermore, Meyers and Meyers (1995) also noted

moderate correlations between RCFT Copy and RCFT Recall performance. The greater improvements seen in the recall trials of the intervention group, thus could be attributed to a more efficient constructing and organisation strategies during the copy trial and this improved approach had potentially assisted in the subsequent recall of the complex figure.

In terms of verbal memory performance, the gain score of the intervention participants on CVLT-II Short Delayed Recall approached significance, along with a large effect size. No significant intervention effect was observed for the RI-48 and Story Recall. The lack of significance on these tests may be partly due to a relatively intact performance on pre-intervention assessments. Despite previous studies suggesting that RI-48 and Story Recall as sensitive measures for early AD (Adam et al., 2007; Rabin et al., 2009), most our MCI participants performed within the normal range compared to others of similar age (i.e., did not fall below a z-score of -1.5).

6.4.5 *Beneficial Effects on Other Cognitive Domains*

The Cognitive Enrichment Programme was employed to stimulate a range of cognitive functions, hence it was expected that the programme would show beneficial effects on measures of non-memory functions. Neuropsychological results revealed that a number of these measures showed a non-significant trend favouring the intervention group, long with a medium to large effect size. As mentioned, the group difference on the gain score

of RCFT Copy approached significance, which suggests a beneficial effect of the programme on visuospatial and visuoconstruction abilities in MCI. Medium to large effect sizes were observed on several other outcome measures, namely TMT-B, Verbal Fluency, Stroop Interference, SDMT, Digit Span, and Boston Naming. These results suggest positive effects of the programme on executive function, attention and processing speed and language abilities. Larger studies with more power are needed to determine whether these observations are real or due to random variation.

6.5 Summary and Conclusion

Using an RCT design, the current study revealed positive, although generally non-significant, intervention effects in persons with MCI. In general, participants in the intervention group demonstrated reduced cognitive decline compared to the waitlist group. Although most differences between the intervention and waitlist group were not statistically significant, we observed a pattern in which effect sizes for cognitive measures consistently favoured the intervention group. The significant improvement found in BVMT-R Delayed Recall suggests that cognitive enrichment increased the ability to encode and retain visuospatial information in MCI individuals. Delayed recall has been suggested as a reliable neuropsychological marker of detecting MCI at risk for dementia. Thus, improvements in delayed recall following intervention are likely to have clinical validity in MCI by protecting those cognitive functions that are most likely to deteriorate. In summary, findings of our randomised controlled pilot study suggest

positive effects of the Cognitive Enrichment Programme in elderly with MCI, and that cognitive enrichment could be a valuable method for supporting cognition in MCI, potentially delaying the progression to AD.

CHAPTER 7 - Cognitive Enrichment Outcomes: Magnetic Resonance Imaging

7.1 Introduction

This chapter explored enrichment-related changes in default mode network (DMN) activity and connectivity in older adults with MCI. As mentioned in Chapter 3, the DMN is defined as a set of brain regions that show a high level of activity when the mind is not engaged in specific behavioural tasks. Its activity is increased during internally directed self-referential cognitive processes (e.g., tasks that require awareness of a personal past, present, and future), but deactivated during tasks that demand external attention (e.g., working memory tasks) (Buckner et al., 2008; Dixon et al., 2014). Neuropathology in the DMN have been repeatedly shown in AD as well as MCI (Bai et al., 2008; Greicius et al., 2004; Hedden et al., 2009; Rombouts et al., 2005; Sorg et al., 2007). The most consistent functional DMN impairment in both MCI and AD is decreased resting-state functional connectivity within the posterior DMN, especially the posterior cingulate cortex (Agosta et al., 2012; Hafkemeijer et al., 2012; Sorg et al., 2007), and a decreased ability to suppress activity within the DMN when performing cognitively demanding tasks (Rombouts et al., 2005). Furthermore, these alterations were found to be related to the severity of the disease and conversion of MCI to dementia (Binnewijzend et al., 2012; Greicius et al., 2004; Petrella et al., 2011).

The Cognitive Enrichment Programme was developed so as to restore (i.e., return to a normal state) or to compensate for (i.e., reduce further decline) functional decline of the DMN in MCI participants. As DMN integrity is marker of cognitive dysfunction of early AD, we used DMN activity and connectivity as an objective measure to assess whether the Cognitive Enrichment Program would have a positive effect on brain function. Two types of functional Magnetic Resonance Imaging (fMRI) procedures were used to examine enrichment-related changes in DMN. One explored task-related activations and deactivations within regions of the DMN (task fMRI), and the other focused on the degree of connectivity of the DMN at rest (resting-state fMRI).

7.2 Method

While all participants (13 MCI and 11 healthy controls) received an MRI scan prior to the start of the Cognitive Enrichment Programme, only the MCI participants were scanned at the end of their enrichment/waitlist period (demographic characteristics of the MCI and HC participants are presented in Table 6-1). Funding was not available for repeat scans on the healthy controls. All scans included structural, functional, diffusion, and arterial spin labelling MR imaging of the brain. Data collection and analyses for the functional MRI scans are described below; structural, diffusion imaging and arterial spin labelling components of this study have not been included in this thesis.

7.2.1 *MRI Acquisition*

MR images were acquired on a 3 tesla General Electric HDxt scanner with an eight channel head coil. Structural MR images included a T1-weighted, three-dimensional spoiled gradient recalled echo (SPGR) acquisition (TE/TR = 2.84/6.7ms, TI = 400ms, flip angle = 15°, acquisition matrix = 256×256×184, FOV = 250mm, slice thickness = 1mm, voxel size = 0.98×0.98×1.0mm³). A T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence for classification of white matter hyperintensities (TE/TR/TI = 105/9000/2250ms, 3mm slices with 1.5mm gap, 33 slices, FOV = 220mm, acquisition matrix = 320×320).

Functional images (both resting state and task) were acquired using a two-dimensional gradient echo, echo planar imaging (EPI) sequence (TE/TR = 35/3000ms, flip angle 90°, acquisition matrix = 64×64×44, FOV = 220mm, slice thickness = 3mm, number of slices = 44, space between slices = 0mm, voxel size = 3.4×3.4×3mm³, interleaved bottom to top, angled 20° above the anterior commissure-posterior commissure line to improve signal from the temporal lobe). A gradient echo field map acquired at two different echo times (TE1/TE2 = 5.3/7.6ms, TR = 475ms) was used to minimise distortion due to susceptibility in homogeneity in the fMRI EPI acquisitions. Resting-state images were acquired over 8 minutes 12 seconds during which time participants were instructed to relax and close their eyes, but stay awake. Task fMRI images were acquired over two 10 minutes 12 seconds sessions; participants were instructed to make yes/no decisions using the MR-safe response pad in the scanner.

7.2.2 Task fMRI Paradigms

Participants were asked to perform two tasks: one to deactivate the DMN (n-back), and the other to activate the DMN (self-reflection). Participants practiced these tasks on a standalone computer before going into the scanner. Each task consisted of an active condition (e.g., two-back; self-reflection) and a control condition (x-not-x; short or long) presented in blocks. Participants were prompted with an instruction screen to inform them about the task/condition to which they should respond on each trial (refer to Figure 7-1 and Figure 7-2). Each task/condition had a different colour border to aid discrimination between tasks/conditions. Participants performed six blocks of each condition, within which they alternated between the active condition and the control condition. Each block (i.e., active or control) started with an instruction screen shown for 9 seconds and ended with 15 seconds of fixation, and contained nine stimuli, presented one at a time for 2.7 seconds, followed with a brief dot shown for 0.3 seconds. The tasks were designed using E-Prime 2.0 software (Psychology Software Tools, www.pstnet.com). The order of runs (the tasks as well as the conditions within the tasks) was counterbalanced across participants. Responses were made with a two-button response device held in the right hand; participants were instructed to use the index finger for yes responses, the middle finger for no responses.

N-Back Task. In the n-back task, fragmented capital letters (70% completed) were presented one at a time in each block (Figure 7-1). Fragmented letters ensured that the precise visual stimulus for any given letter was never repeated while simplifying the task

for the participant. In the active condition (two-back), participants had to remember the letters appearing on a screen and indicate through a button press response if the currently shown letter was identical to the letter presented two trials previously. In the control condition (x-not-x), participants were asked to indicate whether the current fragmented capital letter shown was an x or not, and again indicate yes/no with a button press. Refer to Appendix E for task instructions.

Self-Reflection Task. In the active condition of the self-reflection task, participants responded to a variety of adjectives in each block requiring knowledge of and reflection of their own personalities (e.g., casual, demanding, irritating; Figure 7-2). Participants were instructed to make the decision based on their own opinion of themselves, not someone else's view. In the control condition (short/long), participants made decisions about whether the word shown was a short or a long word. In both conditions, yes/no responses were required by a button press. Trait adjectives presented were obtained from the Anderson (1968). Refer to Appendix E for task instructions.

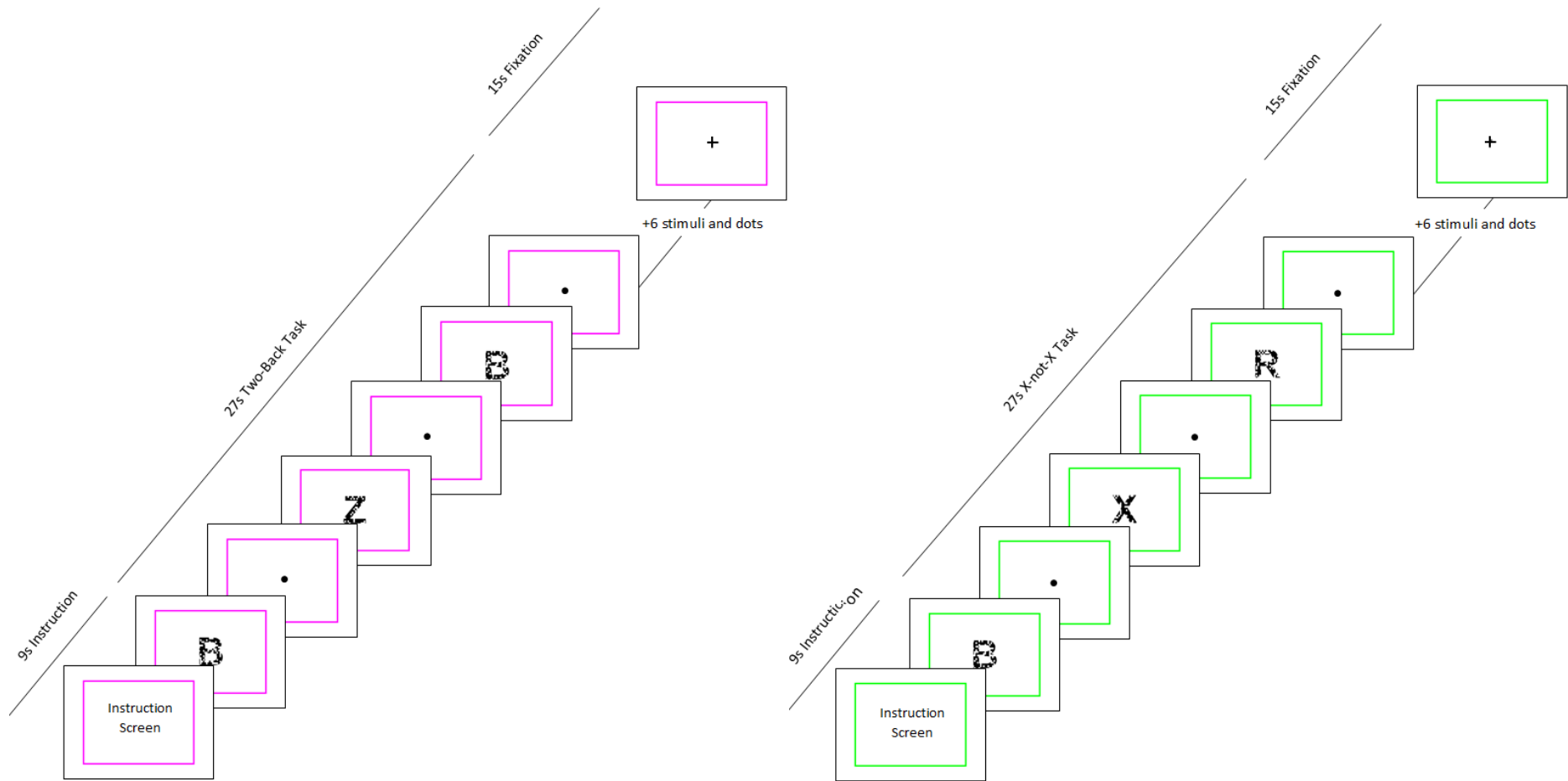


Figure 7-1. Design of the fMRI n-back task, with the active condition (two-back) on the left and the control condition (x-not-x) on the right

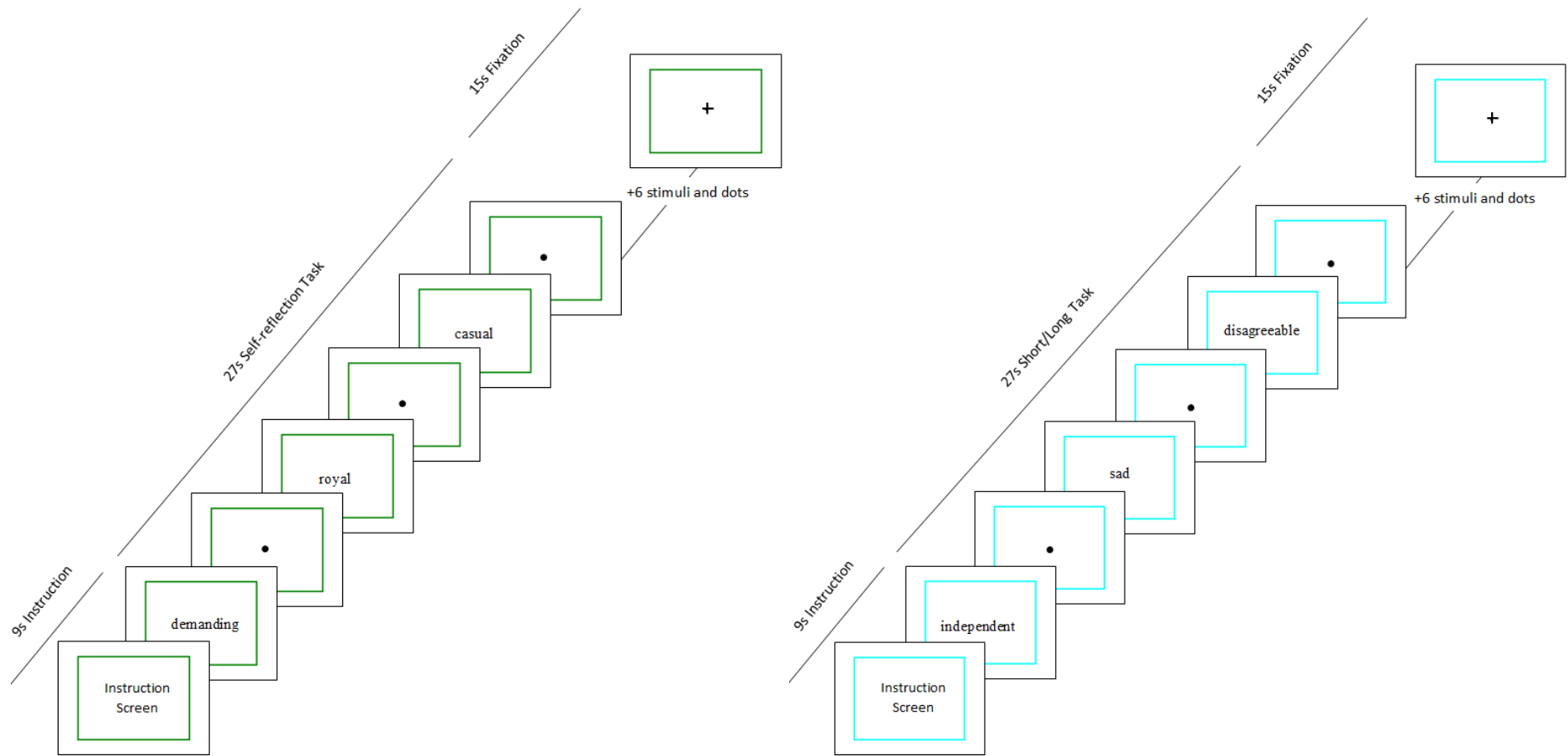


Figure 7-2. Design of the fMRI self-reflection task, with the active condition (self-reflection) on the left and the control condition (short/long) on the right

7.2.3 *MRI Pre-Processing*

Image pre-processing was performed using Statistical Parametric Mapping software (SPM12b v5581; <http://www.fil.ion.ucl.ac.uk/spm/>) implemented in Matlab (R2010a, Mathworks Inc., MA, USA).

For each MCI individual, pre- and post-intervention structural images were aligned to a subject-specific halfway space between the two using the longitudinal registration utility with default parameters (Ashburner & Ridgway, 2012). The mid-point average image for each individual was then segmented and grey matter (GM) atrophy rate images produced by multiplying the native space GM segments (both pre- and post-intervention) by the Jacobian rate. We then ran DARTEL (existing template) using the DARTEL template provided with the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>). This template is in MNI space and is derived from 550 individuals across a wide age range, which is a more representative template than one that could be created from our 24 subjects.

As opposed to MCI, healthy controls underwent only a single imaging session. To ensure control images underwent the same processing and interpolation steps as the MCI scans, which had two time-points, an additional pre-processing step was performed for the healthy control scans. A mirror reversed image was created from the baseline structure image of each healthy control participant and this mirrored image was then used

as the post-intervention structural image and the subsequent processing steps processed as per the MCI processing (Bernal-Rusiel et al., 2013). This method allowed us to evaluate healthy control scans in the longitudinal stream (instead of cross-sectionally), reducing bias and allowing for more faithful comparisons between the groups.

Both task fMRI sessions and the resting-state sessions were processed in a similar fashion, as follows. The FieldMap utility in SPM was used to create a fieldmap and voxel displacement map. A mean functional image was also produced. Functional images were then realigned (motion-corrected to the first functional volume) and unwarped (to minimise susceptibility distortions). This was followed by slice timing correction. At each time point, functional images were then coregistered to the individual's structural brain image using the mean functional image as the source image (mean pre-intervention functional image to pre-intervention structural and mean post-intervention functional to post-intervention structural). In each individual, deformation fields mapping either pre-intervention or post-intervention structural images to the mid-point average were combined with the DARTEL flow fields to normalize the coregistered, slice timing-corrected, realigned, and unwarped functional images at each time point. Lastly, these images were smoothed with an 8 mm isotropic Gaussian kernel.

7.2.4 *Analysis of DMN Activations and Deactivations*

In the first-level (the subject-level), the following parameters were used; inter-scan interval 3s, Microtime Resolution 44, and Microtime Onset 22s. Low frequency drifts were removed using a temporal high-pass filter with a cut-off of 128s. Serial autocorrelation was also corrected using autoregressive model. Six contrast images were created for each subject (control condition > active condition; active condition > control condition; control condition > fixation; fixation > control condition; active condition > fixation; fixation > active condition). These subject-specific summaries of activation/deactivation were then taken to second-level analyses. Given the sample size, a height threshold of $p < 0.001$, uncorrected for multiple comparisons across the whole brain was applied, with $k > 10$ voxels.

7.2.5 *Analysis of the Resting-State DMN Functional Connectivity*

To identify the DMN, smoothed, normalized resting state images for all participants were entered into a group Independent Component Analysis (ICA) using the Group ICA fMRI Toolbox (GIFT; <http://icatb.sourceforge.net>) implemented in Matlab. Twenty independent components were estimated using the infomax algorithm, with default parameters. All components were then spatially correlated with a healthy control template provided by S. M. Smith et al. (2009) (Figure 7-3). The component with the highest spatial correlation to the DMN template was selected for further analysis. The individual DMN component maps were transformed to z-scores, using the following formula:

$$C_z(X) = (C(X) - \mu_c) / \sigma_c$$

where $C(X)$ are the component weightings within each selected DMN image, μ_c is the mean and σ_c is the standard deviation of component weightings in the map, and $C_z(X)$ represents the z scored component weighting (Greicius et al., 2004; Petrella et al., 2011).

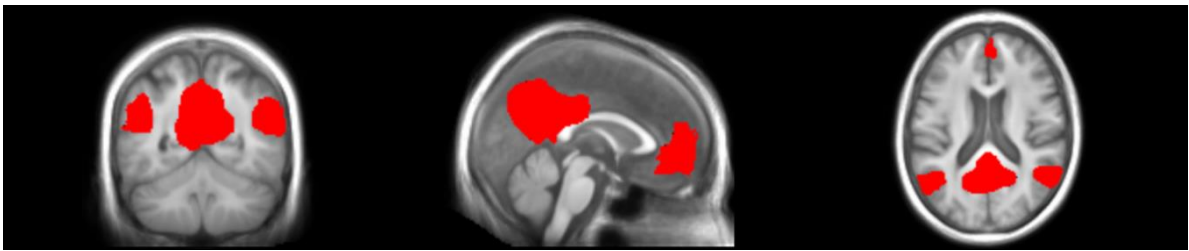


Figure 7-3. DMN template from Smith et al., (2009).

A goodness-of-fit (GOF) index was then calculated. The GOF index reflected the degree to which each individual's DMN matched the healthy DMN template provided by S. M. Smith et al. (2009). For each individual's DMN component, the GOF was calculated as the difference between the mean z-score of all voxels that fell inside the DMN template (z inside) and the mean z-score of all voxels outside the DMN template (z outside); that is $GOF = \text{mean}(z \text{ inside}) - \text{mean}(z \text{ outside})$ (Greicius et al., 2004; Petrella et al., 2011).

7.2.6 Statistics on GOF

GOF values were compared across time and group using linear mixed-effects models with the *nlme* package in R (v3.0.0). Baseline age, sex and time between scans were included in the model.

7.3 Results

7.3.1 Task fMRI: N-Back (Baseline Scans: Healthy Control and MCI)

Repeated measure *t*-tests were conducted to examine the task effect within the healthy control and MCI group.

Two-Back vs. X-not-X. For the two-back > x-not-x contrast, increased activation was observed in the inferior parietal lobule, middle frontal gyrus, inferior frontal gyrus, fusiform gyrus, thalamus and cerebellum (red regions in Figure 7-4; Table 7-1). For the x-not-x > two-back contrast, the only region that showed more activation during the x-not-x condition was the superior temporal gyrus (blue regions in Figure 7-4; Table 7-1).

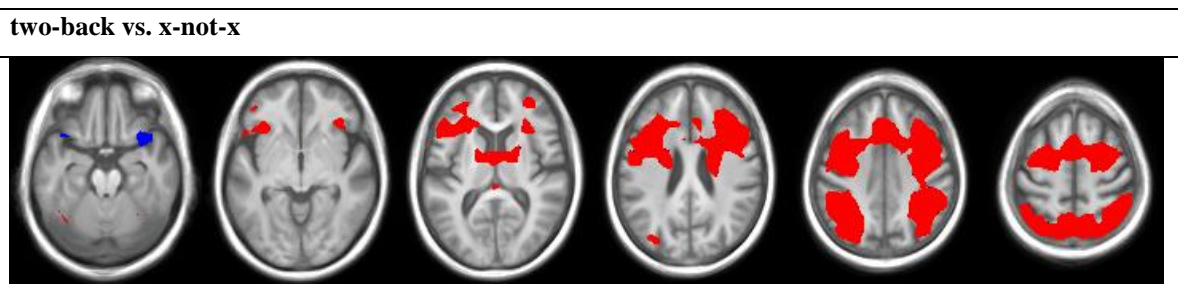


Figure 7-4. Brain regions showing significant fMRI response to two-back relative to x-not-x. Axial slices $z = 35, 45, 55, 65, 75, 85$. Red = areas of activation (two-back > x-not-x). Blue = areas of deactivation (x-not-x > two-back). Uncorrected $p < 0.001$; $k > 10$.

Two-Back vs. Fixation. The two-back > fixation contrast revealed increased activation in the supplementary motor area, inferior parietal lobule, middle occipital gyrus, middle temporal gyrus, supramarginal gyrus and cerebellum (red regions in Figure

7-5; Table 7-1). For the contrast of fixation > two-back, increased activation was observed in the posterior cingulate gyrus and precuneus (blue region in Figure 7-5; Table 7-1). The posterior cingulate gyrus and precuneus are known to be part of the DMN.

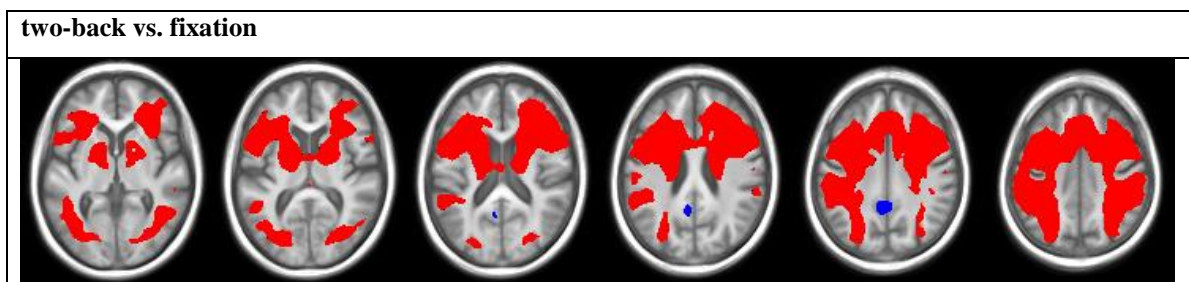


Figure 7-5. Brain regions showing significant fMRI response to two-back relative to fixation. Axial slices $z = 50, 55, 60, 65, 70, 75$. Red = areas of activation (two-back > fixation). Blue = areas of deactivation (fixation > two-back). Uncorrected $p < 0.001$; $k > 10$.

X-not-X vs. Fixation. The x-not-x > fixation contrast revealed increased activation in the postcentral gyrus, middle occipital gyrus, middle temporal gyrus, supramarginal gyrus, superior parietal gyrus, inferior frontal gyrus, putamen and cerebellum (red regions in Figure 7-6; Table 7-1). As above (fixation > two-back), there were activations in regions that overlapped with the DMN for the contrast of fixation > x-not-x, including the precuneus, posterior cingulate gyrus and hippocampal formation (blue regions in Figure 7-6; Table 7-1).

x-not-x vs. fixation

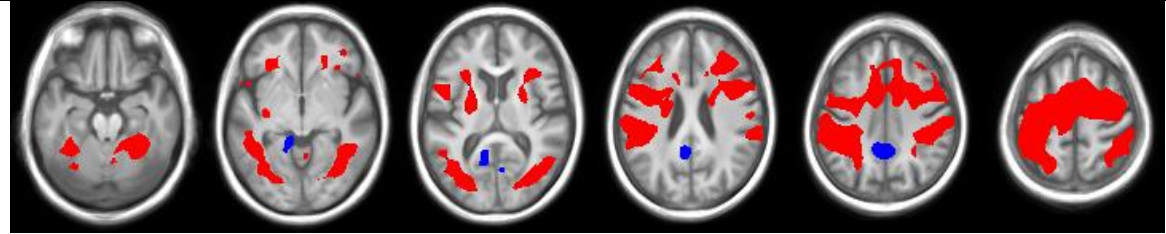


Figure 7-6. Brain regions showing significant fMRI response to x-not-x relative to fixation. Axial slices $z = 35, 45, 55, 65, 75, 85$. Red = areas of activation ($x\text{-not-}x > \text{fixation}$). Blue = areas of deactivation ($\text{fixation} > x\text{-not-}x$). Uncorrected $p < 0.001$; $k > 10$.

Table 7-1

Regions of Activations and Deactivations Associated with the N-Back Task (baseline scans: healthy control and MCI)

Regions	Coordinates			z-score
	x	y	z	
Two-Back vs. X-not-X				
two-back > x-not-x				
R inferior parietal lobule	47	-51	44	5.97
L middle frontal gyrus	-36	3	50	5.85
L inferior fontal gyrus	-45	42	-9	3.99
R cerebellum	32	-51	-27	3.65
L fusiform gyrus	-39	-62	-21	3.33
L thalamus	-11	-6	-3	3.26
x-not-x > two-back				
R superior temporal gyrus	40	21	-30	4.25
L superior temporal gyrus	-44	9	-18	3.64
Two-Back vs. Fixation				
two-back > fixation				
L supplementary motor area	-6	1	51	7.27
L inferior parietal lobule	-50	-33	45	6.55
R middle occipital gyrus	33	-80	3	5.98
R middle temporal gyrus	42	-71	0	5.39
R cerebellum	30	-50	-24	4.90
R supramarginal gyrus	59	-36	24	3.51
fixation > two-back				
L posterior cingulate gyrus	-5	-50	32	4.13
L precuneus	-2	-61	20	4.15
X-not-X vs. Fixation				
x-not-x > fixation				
L postcentral gyrus	-39	-29	54	6.77
R middle occipital gyrus	39	-74	2	5.98
L middle occipital gyrus	-38	-77	-1	5.72
R middle temporal gyrus	50	-63	5	5.47
L cerebellum	-35	-47	-27	5.22
R supramarginal gyrus	57	-23	39	5.15
R superior parietal gyrus	41	-51	59	4.39
L putamen	-33	-15	-6	4.17
R inferior frontal gyrus	49	42	-10	3.81
fixation > x-not-x				
L precuneus	-6	-48	38	4.28
L lingual gyrus	-9	-44	-1	4.03
L posterior cingulate gyrus	-6	-50	24	3.95
R calcarine gyrus	6	-78	17	3.71
L hippocampus	-20	-17	16	3.54
L angular gyrus	-50	-72	32	3.38
L parahippocampal gyrus	-18	-30	-13	3.24

Note. Peak z-scores, corresponding to uncorrected p-values and MNI coordinates (x, y, z) of deactivated brain regions; L = left; R = right; threshold for statistical significance $p < 0.001$, uncorrected for multiple comparisons, $k > 10$ voxels.

7.3.2 Task fMRI: Self-Reflection (Baseline Scans: Healthy Control and MCI)

Repeated-measure *t*-tests were conducted to examine the task effect within the healthy control and MCI group.

Self-Reflection vs. Short/Long. For the contrast of self-reflection > short/long, there were activations in regions that overlapped with the DMN (Red regions in Figure 7-7; Table 7-2). These regions included the precuneus, angular gyrus, posterior cingulate gyrus, and medial frontal gyrus. Additional areas of activation included the fusiform gyrus, inferior frontal gyrus, superior frontal gyrus, lingual gyrus, middle temporal gyrus, superior temporal gyrus and supramarginal gyrus. For the short/long > self-reflection contrast, only three regions exhibited increased activity, the superior parietal gyrus, the superior occipital gyrus, and middle temporal gyrus (blue region in Figure 7-7; Table 7-2).

self-reflection vs. short/long

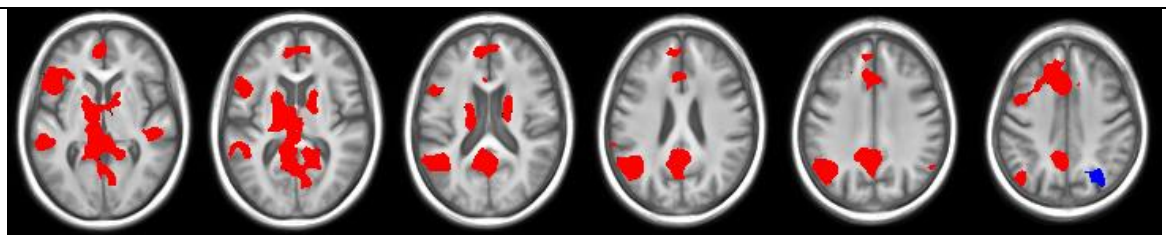


Figure 7-7. Brain regions showing significant fMRI response to self-reflection to short/long. Axial slices $z = 50, 55, 60, 65, 70, 75$. Red = areas of activation (self-reflection > short/long). Blue = areas of deactivation (short/long > self-reflection). Uncorrected $p < 0.001$; $k > 10$.

Self-Reflection vs. Fixation. The contrast of self-reflection > fixation showed increased activation in the supplementary motor area, putamen, supramarginal gyrus, inferior parietal lobule, superior parietal gyrus, and middle occipital gyrus (red regions in Figure 7-8; Table 7-2). The fixation > self-reflection contrast revealed increased activation in the precuneus (blue regions in Figure 7-8; Table 6-2).

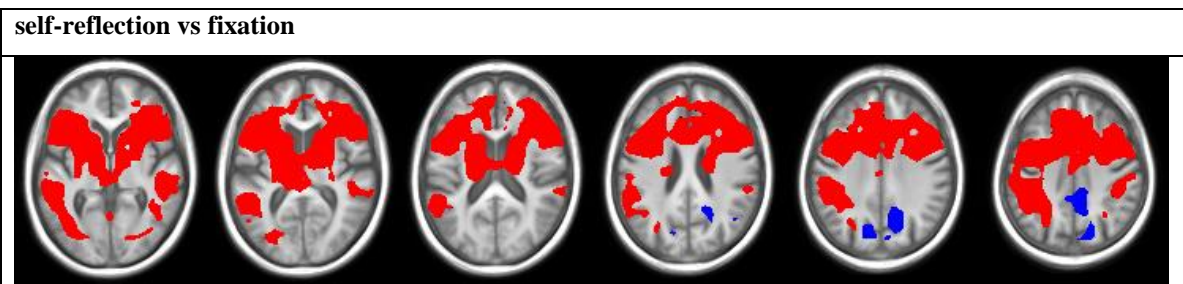


Figure 7-8. Brain regions showing significant fMRI response to self-reflection relative to fixation. Axial slices $z = 50, 55, 60, 65, 70, 75$. Red = areas of activation (self-reflection > fixation). Blue = areas of deactivation (fixation > reflection). Uncorrected $p < 0.001$; $k > 10$.

Short/Long vs. Fixation. For the short/long > fixation contrast, increased activation was observed in the superior parietal gyrus, superior occipital gyrus, middle temporal gyrus, superior temporal gyrus, middle temporal gyrus and cerebellum (red regions in Figure 7-9; Table 7-2). The fixation > short/long contrast revealed increased activation in regions that are known to be part of the DMN. These regions included the posterior cingulate gyrus, precuneus, angular gyrus, medial frontal gyrus, and hippocampus (blue regions in Figure 7-9; Table 7-2).

short/long vs. fixation

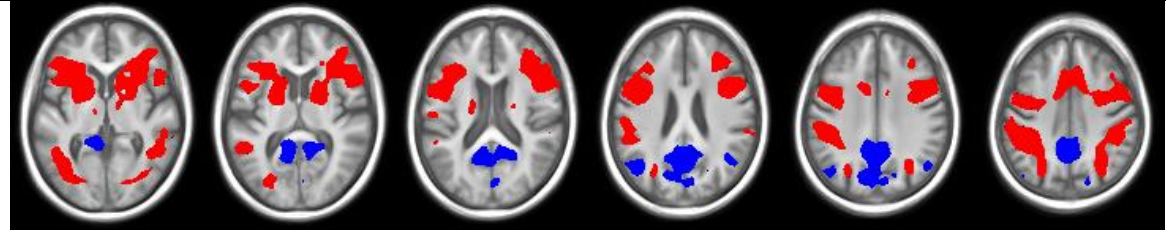


Figure 7-9. Brain regions showing significant fMRI response to short/long relative to fixation. Axial slices $z = 35, 45, 55, 65, 75, 85$. Red = areas of activation (short/long > fixation). Blue = areas of deactivation (fixation > short/long). Uncorrected $p < 0.001$; $k > 10$.

Table 7-2

Regions of Activations and Deactivations Associated with the Self-Reflection Task (baseline scans: healthy control and MCI)

Regions	Coordinates			z-score
	x	y	z	
Self-Reflection vs. Short/Long				
self-reflection > short/long				
R angular gyrus	59	-60	30	3.56
L angular gyrus	-44	-59	29	5.42
L posterior cingulate gyrus	-3	-46	30	5.59
L fusiform gyrus	-44	-50	-24	4.01
L inferior frontal gyrus	-53	22	-6	4.86
R lingual gyrus	29	-68	-3	3.41
L middle temporal gyrus	-44	-54	14	4.61
L precuneus	-6	-51	18	5.31
L superior frontal gyrus	-3	3	62	5.07
L medial frontal gyrus	-3	60	-4	4.39
R superior temporal gyrus	54	17	-24	4.99
L superior temporal gyrus	-45	16	-33	3.57
L supramarginal gyrus	-65	-39	24	3.33
short/long > self-reflection				
R superior occipital gyrus	33	-71	41	3.64
R superior parietal gyrus	38	-65	54	3.60
R middle temporal gyrus	54	-48	-3	3.70
Self-Reflection vs. Fixation				
self-reflection > fixation				
R middle occipital gyrus	30	-63	36	3.59
L putamen	-17	4	3	6.95
R supplementary motor cortex	8	4	57	7.16
R supramarginal gyrus	47	-33	42	4.78
R superior parietal gyrus	33	-62	57	3.59
fixation > self-reflection				
R precuneus	8	-54	38	4.32
L precuneus	-11	-75	28	3.52
Short/Long vs. Fixation				
short/long > fixation				
R supplementary motor area	9	-11	65	6.40
R superior parietal gyrus	33	-62	53	5.24
L superior parietal gyrus	-27	-65	48	6.28
R superior occipital gyrus	32	-69	41	5.34
R middle temporal gyrus	54	-45	-4	5.12
R superior temporal gyrus	60	-33	23	3.34
R middle frontal gyrus	28	53	-6	3.28
fixation > short/long				
R angular gyrus	48	-65	29	3.92
L angular gyrus	-48	-74	32	3.77
L posterior cingulate gyrus	-6	-47	3	4.85
R precuneus	2	-54	35	4.71
R medial frontal gyrus	9	-6	51	5.31
R superior occipital gyrus	24	-69	21	3.35
L hippocampus	23	-15	-15	3.31

Note. Peak z-scores, corresponding to uncorrected p-values and MNI coordinates (x, y, z) of the activated brain regions; L = left; R = right; threshold for statistical significance $p < 0.001$, uncorrected for multiple comparisons, $k > 10$ voxels.

7.3.3 *Task fMRI: Group Effect (Baseline Scans: Healthy Control vs. MCI)*

Two-sample *t*-tests were conducted to examine the group difference between the healthy control and MCI participants. For the both tasks (n-back and self-reflection), there were no significant differences in patterns of brain activation or deactivation between healthy control and MCI participants for any of the contrasts of interest.

7.3.4 *Task fMRI: Enrichment-Related Changes (Pre- and Post-Scans: MCI only)*

In order to investigate enrichment induced changes in DMN activation/deactivation, repeated-measure ANOVA (i.e., flexible factorial model in SPM 12) with within-subject factor time (pre, post) and between-subject factor group (intervention, waitlist) was performed. The results [intervention (post > pre) > waitlist (post > pre)] showed no significant enrichment-related changes in brain activity during the n-back or the self-reflection task.

7.3.5 *Resting-State fMRI: Group Effect (Baseline Scans: Healthy Control and MCI)*

GOF analysis of DMN functional connectivity at baseline showed no group difference between healthy control and MCI participants [$F(1, 9) = 0.10$; $p = 0.33$]. The means were 1.54 ($SD = 0.25$) for the healthy control group and 1.40 ($SD = 0.23$) for the MCI group (Figure 7-10).

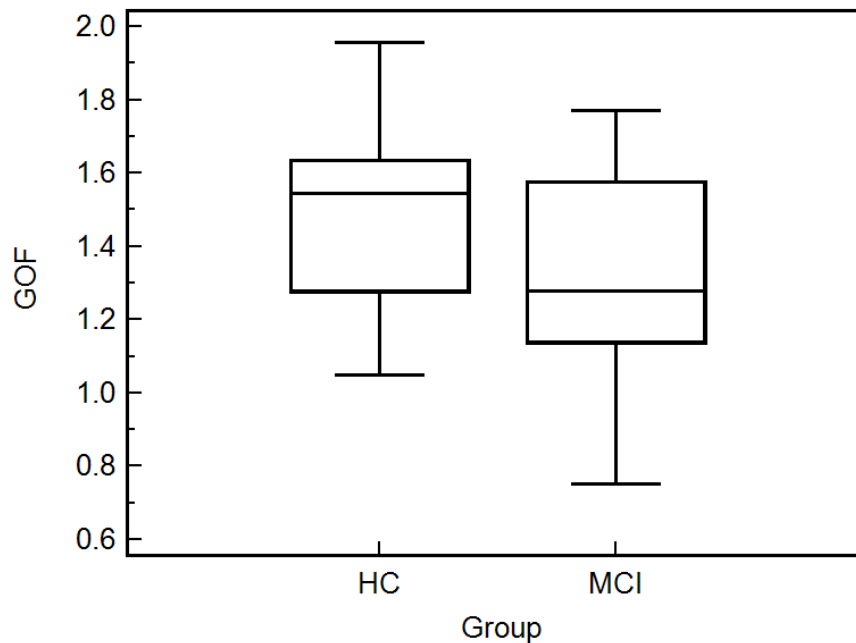


Figure 7-10. Box whisker plot of GOF of HC and MCI participants at baseline. GOF = Goodness of Fit; HC = Healthy Control. Plot depicts the median, interquartile range, and range of values for each group.

7.3.6 Resting-State fMRI: Enrichment-Related Changes (Pre- and Post-Scans: MCI only)

Linear mixed effects modelling was conducted to determine the effects of the Cognitive Enrichment Programme on the DMN functional connectivity using the GOF value. The primary finding was an interaction between group and time, which just failed to reach statistical significance, after controlling for age, sex and time between scans [$F(1, 11) = 2.19, p = 0.051$]. Compared to pre-intervention, an increase in DMN functional connectivity (indicated by higher GOF) was found for the intervention group, while a decrease was observed for the waitlist group (Table 7-3 and Figure 7-11). Figure 7-12 shows changes in individual GOF scores over time. Baseline GOF values did not differ

significantly between the intervention waitlist groups [$F(1, 9) = 0.54, p = 0.60$].

Additionally, there was no significant main effect of sex [$F(1, 9) = 1.26, p = 0.24$], or age [$F(1, 9) = 0.79, p = 0.45$].

Table 7-3
Group Mean (SD) GOF Values Pre-and Post-Cognitive Enrichment

	Pre-Intervention GOF	Post-Intervention GOF
	Mean (SD)	Mean (SD)
Intervention MCI ($n = 6$)	1.26 (0.30)	1.50 (0.32)
Waitlist MCI ($n = 7$)	1.54 (0.34)	1.21 (0.42)

Note. GOF = Goodness of Fit; MCI = Mild Cognitive Impairment; SD = Standard Deviation.

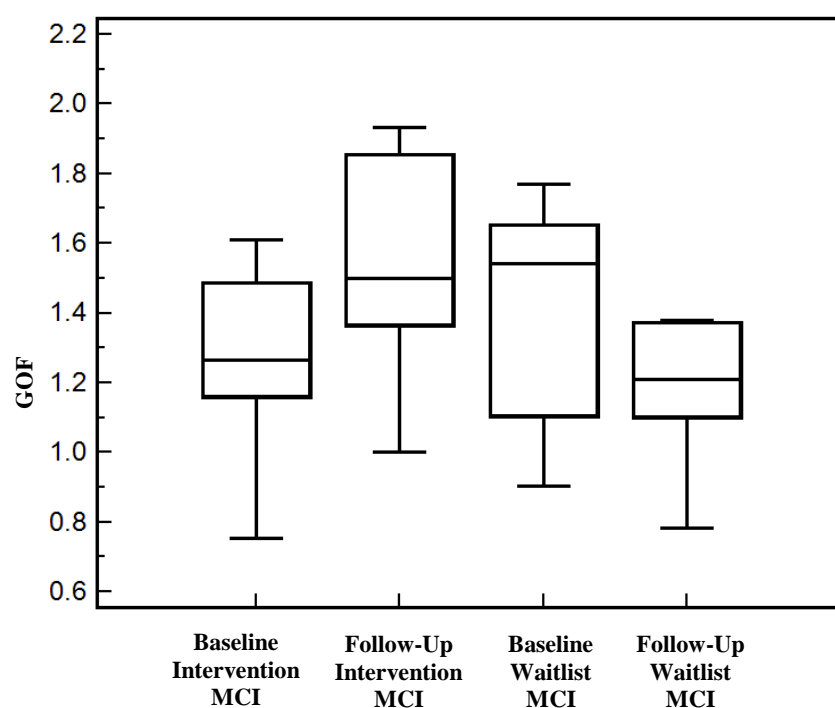


Figure 7-11. GOF values at baseline and follow-up for intervention and waitlist participants. GOF = Goodness of Fit; MCI = Mild Cognitive Impairment. Plot depicts the median, interquartile range, and range of values for the intervention and waitlist group at pre- and post-enrichment.

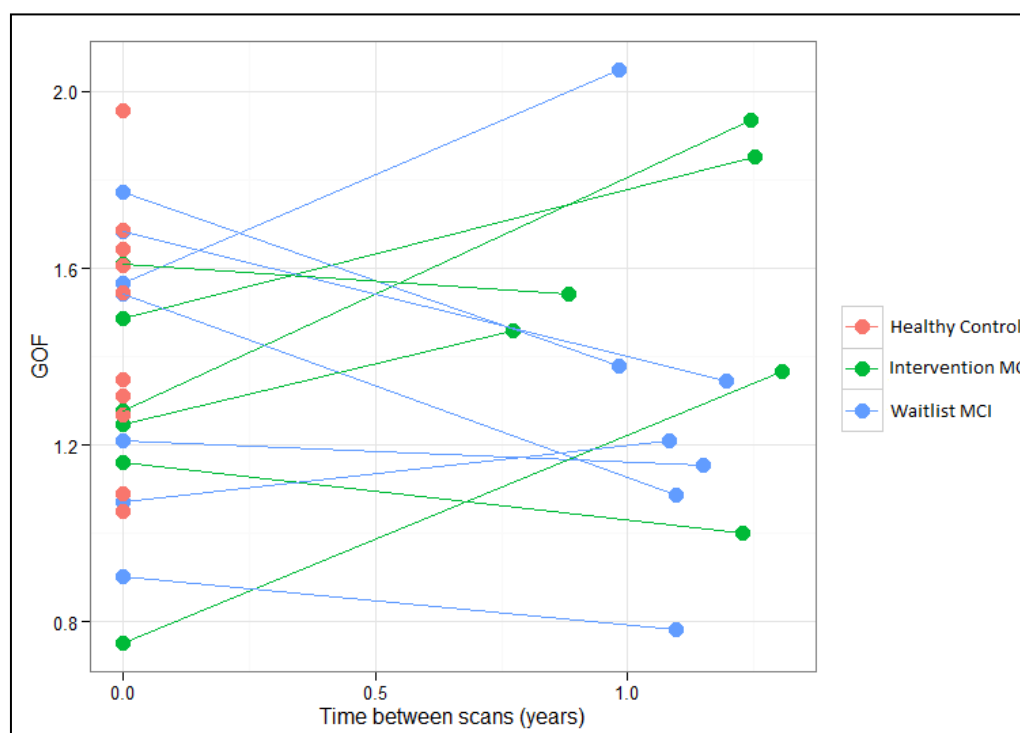


Figure 7-12. Changes in individual GOF scores over time. Red dots = Healthy Control; Green dots = Intervention MCI; Blue dots = Waitlist MCI. GOF = Goodness of Fit. Line between dots indicates changes in GOF values over time. The variation in time between scans was included as a covariate in the statistical model.

7.3.7 Correlation Between GOF Changes and Cognitive Performance

We determined whether the GOF changes that occurred between pre- and post-intervention scans were associated with changes on primary neuropsychological measures. Changes in GOF were found to be significantly correlated with the improvement on the Verbal Fluency test ($r = 0.57, p < 0.05$; Figure 7-13). None of the other tests correlated significantly with changes in GOF (Table 7-4), but the correlation approached significance for Stroop Interference ($r = 0.53, p = 0.06$; Figure 7-14).

Table 7-4
Correlation between Neuropsychological Measures and Changes in GOF

	<i>r</i>	<i>p</i>
Executive Function		
Verbal Fluency	0.57	0.04
Category Fluency	0.07	NS
Category Switching	0.36	NS
Stroop Interference	0.53	NS
Design Fluency Filled Dots	-0.18	NS
Design Fluency Empty Dots	-0.44	NS
Design Fluency Switching	-0.44	NS
Attention and Processing Speed		
SDMT	0.41	NS
Stroop Colour Naming	-0.25	NS
Stroop Word Naming	-0.02	NS
Learning and Memory		
BVMT-R Total Recall	0.19	NS
BVMT-R Delayed Recall	0.20	NS
Story Immediate Recall	-0.30	NS
Story Delayed Recall	0.06	NS

Note. SDMT = Symbol Digit Modalities Test; BVMT-R = Brief Visuospatial Memory Test-Revised.

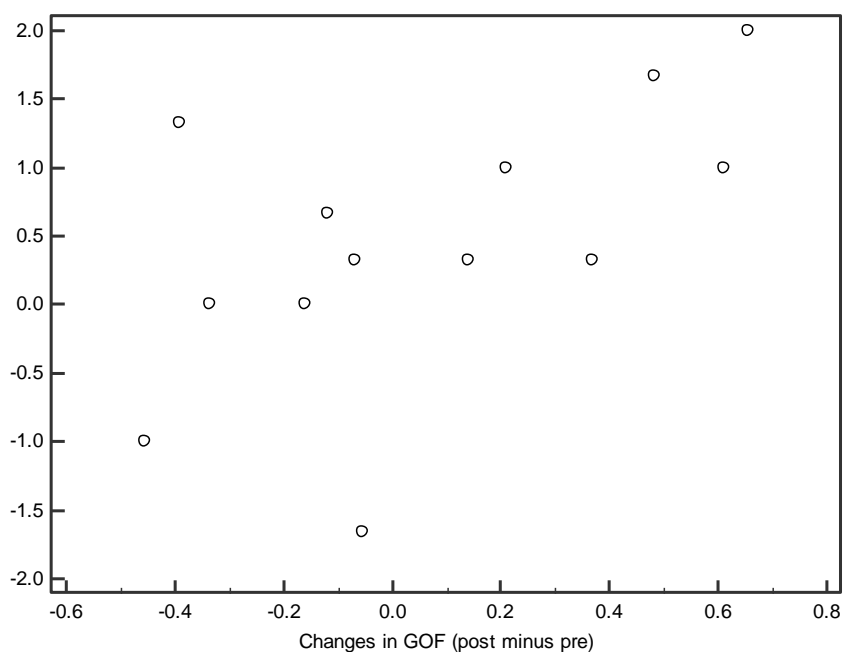


Figure 7-13. Correlation between the changes in GOF indices and changes in Verbal Fluency performance in MCI.

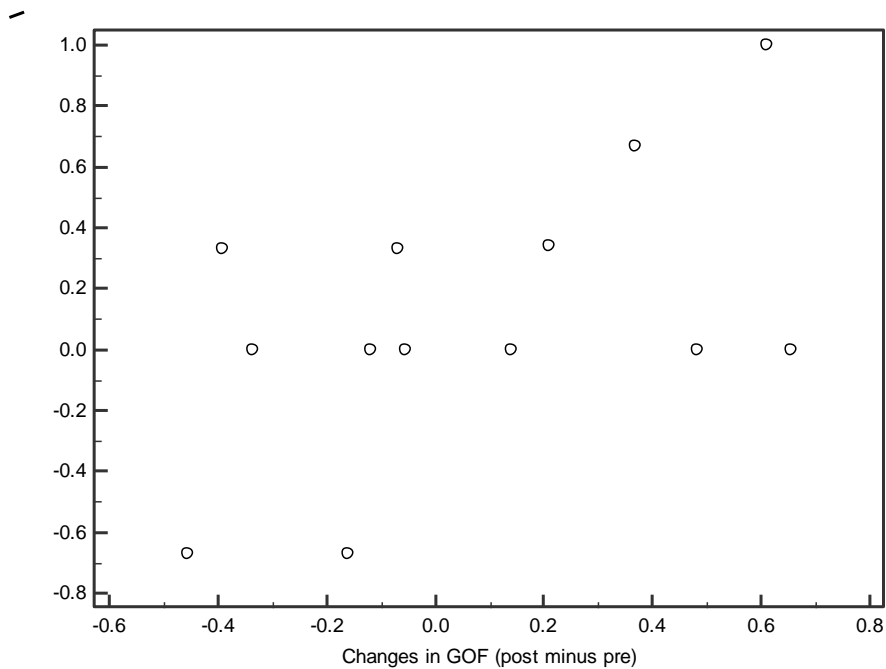


Figure 7-14. Correlation between the changes in GOF indices and changes in Stroop Inference performance in MCI.

7.4 Discussion

In this chapter we investigated the effect of cognitive enrichment on brain function, with a focus on its effect on the DMN. The results demonstrated that cognitive enrichment was associated with an outcome of enhanced resting-state functional connectivity within regions of the DMN by comparison with MCI participants who remained on a waitlist. Following cognitive enrichment the intervention group showed an increase in the mean GOF, while that the waitlist group decreased. It should be noted that the group x time interaction only just failed reach statistical significance, and despite the small sample size. Previous research has indicated that GOF indices lie in a continuous range with the highest integrity in normal elderly and MCI participants who remain stable, but low in

individuals with MCI who progress to AD and in AD patients (Petrella et al., 2011), suggesting that changes in GOF indices may correspond to changes in cognitive clinical stages. Hence, the Cognitive Enrichment Programme may represent a viable intervention option to prevent decline of the DMN in individuals with MCI. However, studies with larger sample sizes are required to validate this finding.

To understand the relevance of changes in functional connectivity to cognition, we assessed the association between changes in GOF and performance on standardised neuropsychological measures. In contrast to previous studies suggesting a close association between DMN and episodic memory processes (Greicius et al., 2004; McCormick et al., 2014; Sestieri, Corbetta, Romani, & Shulman, 2011), we did not find a significant relationship between changes in resting-state DMN functional connectivity and memory performance in our MCI participants. Our results suggested that changes in GOF were correlated with improved performance on the Verbal Fluency test and with the Stroop Interference test. Both tests are measures of executive function, and the successful completion of these tasks requires a high degree of cognitive control. It is assumed that the extent of DMN activity reflects the ability of the brain to redirect its activity from internal (self-focused) to external (goal-directed) processes (Raichle et al., 2001). Impairments in the DMN have been suggested to associate with deficits in interference control, commonly interpreted as a failure to fully and effectively transition from an internal state to an active processing mode during performance of cognitive tasks (Sonuga-Barke & Castellanos, 2007), which results in an intrusion of task-non-specific

cognition (typically seen at rest) into periods of active task-specific processing, producing periodic fluctuations in attention that compete with goal-directed activity. Thus, the correlation between changes in DMN functional connectivity and executive function may be interpreted as a result of improved ability of the DMN to transition between its ‘internal’ and ‘external’ state following cognitive enrichment.

In terms of task fMRI, we found patterns of activation (via the self-reflection task) and deactivation (via the n-back task) that included regions of the DMN in some of the contrasts. However, the extent and intensity of DMN activations/deactivations were lower than what we had initially anticipated. For the n-back task, both task conditions (two-back and x-not-x) produced deactivation in regions of the DMN when compared to fixation, but it was surprising to find in the current study that the two-back > x-not-x contrast did not produce significant DMN deactivation. Even more to our surprise, stronger DMN deactivation was observed in the contrast of x-not-x > fixation than two-back > fixation. Previous studies suggested that increased working memory load is associated with stronger DMN deactivation (Leech & Sharp, 2014; Sambataro et al., 2010). However, this association was not found in the current study. In contrast, our results suggested that a simple discrimination task (i.e., x not x) may be sufficient to elicit DMN deactivation. For the self-reflection task, increased DMN activation was observed in the self-reflection > short/long contrast. This suggests that the self-reflection paradigm used by the current study led to detectable BOLD signal changes in the DMN and is

therefore compatible with previous research suggesting that self-reflection leads to increased DMN activation (Buckner & Carroll, 2007; Ries et al., 2012; Ries et al., 2006).

Cognitive training in MCI has resulted in greater activation within regions of the DMN in previous studies. For example, Hampstead et al. (2011) reported greater activation in within the posterior cingulate cortex, medial frontal cortex and left temporoparietal junction following explicit-memory training. Another study of mnemonic strategy training reported increased activation in the frontal, temporal and parietal areas after episodic memory training (Belleville et al., 2011). In contrast, we did not find such effect with the Cognitive Enrichment Programme. The interpretation of the task fMRI in the current study may be limited by the fact that task performance was not included in the statistical model. Previous studies have reported significant correlations between task performance and levels of brain activity (Fleisher et al., 2009). Resting-state fMRI, in contrast, is not dependent on differential task performance, and thus does not suffer from variability related to task performance.

Although prior studies have demonstrated differences in brain activation/deactivation and resting-state functional connectivity in the DMN in MCI participants compared to healthy controls, we did not find such between-group differences in the current study. There are a number of possible explanations for this lack of difference in our study. First, the relatively small sample size may have attenuated the statistical power to reveal the between-group differences. Second, the differences in

disease characteristics (e.g., level of cognitive impairment) may contribute to increased variability in brain pathology, so it may be useful for future studies to include grey matter in the DMN as a covariate (not measured here). It is likely that many of our MCI participants were in a relatively early stage of MCI, because all of them were recruited from screenings of healthy individuals from the community, rather than from a medical centre or hospital. A study of normal ageing, MCI, and AD demonstrated a nonlinear trajectory of functional MR imaging activation across the continuum of impairment (Celone et al., 2006), which suggests that patients in the late stage of MCI or patients with mild AD are more likely to show distinct patterns of DMN impairments. Third, when running the ICA analysis, we used an independent template of the DMN from S. M. Smith et al. (2009), rather than a template created from our healthy control, as was done in previous studies (Greicius et al., 2004; Petrella et al., 2011). Using a template created from own control subjects is likely to artificially amplify any between-group differences, because the control data would be used to create the template in the first place and therefore would better match the template and produce a higher GOF value.

7.5 Summary and Conclusion

Previous literature suggests that the DMN is impaired with ageing. Our results demonstrated that an intervention program could strengthen the connectivity between regions of the DMN. To our knowledge, this study provides the first evidence of the beneficial effects of cognitive enrichment, as opposed to focused memory training, on the

DMN in individuals with MCI. Our findings are by no means definitive, but rather should serve as a starting point for future research on the relationship between cognitive enrichment and changes in brain networks and their connectivity.

CHAPTER 8 - Concluding Summary and Outlook

8.1 Main Findings

The first contribution of this thesis was that the screening study provided valuable information about the selection of tests and appropriate cut-off scores of potential screening tools for MCI individuals. Our results showed that while MoCA, RCFT Copy and RCFT Recall provided good accuracy for the identification of MCI, TMT-A performed poorly as a screening test. Furthermore, logistic regression analysis revealed that the combination of MoCA and RCFT (copy and 3-min recall) exhibited more useful diagnostic indicators than either the MoCA or RCFT in isolation. The combined model provided excellent discrimination between MCI from normal cognition, plus added diagnostic utility when discriminating MCI from possible MCI. These findings suggest that health professionals should consider including the RCFT as an adjunct test to the more routinely used MoCA when screening for MCI. The use of cognitive screening instruments can have a significant impact on the early detection and treatment of MCI because of the possibility of wide-spread use at the primary care or community level. However, it is important to recognise that the primary purpose of screening is not to confirm diagnosis but to establish the need for an in-depth assessment. Thus, it is necessary to follow up any positive results with comprehensive neuropsychological assessments.

The second contribution of the thesis was the development of the Cognitive Enrichment Programme. The Cognitive Enrichment Programme used a novel approach to cognitive intervention in that enrichment tasks were designed to influence multiple brain networks. Results from the cognitive enrichment study indicated that the enrichment programme we developed is both feasible and has a high potential for reducing further cognitive declines in persons with MCI. The neuropsychological results revealed an intervention effect on a measure of delayed recall of visuospatial information. Although this result might be taken as a chance finding, as other neuropsychological outcome measures did not reach statistical significance. However, the resulting effect sizes were generally in favour of the intervention group, suggesting that a larger sample size might obtain statistical significance. In terms of fMRI results, the enrichment programme was found to improve the functional connectivity of DMN at rest in intervention participants, while the waitlist group showed a reduced connectivity. And, this improved functional connectivity was associated with an improved performance on the Verbal Fluency test in intervention participants. However, no task-related brain activation and deactivation changes were found. Taken together, these results suggest some positive effects of the Cognitive Enrichment Programme on the DMN in MCI, but further studies are required to confirm the efficacy of this intervention programme.

8.2 Critique of the Study and Future Direction

8.2.1 Sample Size

Some limitations of the study should be acknowledged. Firstly, this study has a smaller sample size in comparison to other studies, despite an initial large number of screened participants. Thus, a lack of statistical power may be suspected for the non-significant results. Conversely, the small sample size also precluded more rigorous statistical analysis with control of multiple comparisons. Given the small sample size and the number of statistical analyses conducted, the possibility of a Type I error (e.g., delayed recall) cannot be excluded. Hence, these results should be regarded as promising but preliminary, awaiting confirmation, and as a starting point for further research.

The MCI population, particularly the amnesic subtype, seems difficult to recruit for intervention purposes. Large study samples were scarce in studies reviewed in Chapter 3. Participants with MCI are not easy to find possibly because a large proportion of these individuals is still functionally independent and active (Petersen, 2004), therefore they do not come to the attention of physicians or other health care professionals. In addition, some of them despite acknowledging a cognitive decline could be feeling ambivalent about engaging in such research studies. We also found that when such individuals are interested in the study, their busy social schedules often interfered with their ability to participate in the study. Relatively younger people with MCI may still be

working, thus it could be difficult for them to find enough time in their daily schedule to participate in this kind of research study.

8.2.2 *Control Condition*

A further limitation of the study was the lack of an active control group. Without a control intervention, we cannot determine with certainty whether the observed outcomes were due to the specific components of the intervention or simply as a result of engaging in any forms of activities. However, prior studies have shown that it is difficult to devise an active control condition for this type of study. Barnes et al. (2009) included an active control condition in their study of computer-based cognitive training for MCI. Their intervention programme required participants to determine whether two sounds were sweeping upward or downward; identify a target syllable when it interrupted a repeated, similar sounding syllable; distinguish between two similar sounds/similar sounding words; match sounds on a spatial grid; follow a series of instructions that increased in complexity and identify the picture that correspond to the sentence. The active control condition consisted of listening to audio books, reading online newspaper, and playing a visuospatially oriented computer game. They later found that a few of the outcome measures were in favour of the active control condition, which they attributed this effect to the type of exercises included in their control condition. Therefore, careful planning of the active control group is required to reduce the risk of the condition being too active and thus diluting the intervention effect. Future studies should consider the use of a three-

arm design (an intervention group, an active control group, a no-contact control group), and confirm that any active control activities are, in fact, inert before commencing a trial.

8.2.3 *Generalisation of the Results*

There are a few concerns regarding generalisability of the intervention effects. It is possible that those who enrolled and participated differed from those who declined participation. First, approximately a third of the initial screened sample was excluded based on medication and medical condition reasons. Thus, participants included in the current study are likely to have a better physical health than the general elderly population. That is, it is unclear whether the current results would generalise to individuals with more chronic health conditions. Intervention programmes may be less effective for individuals with chronic health conditions, as these individuals tend to face more demands including managing numerous health appointments, adhering to medications and self-monitoring their conditions (Bohlen, Scoville, Shippee, May, & Montori, 2012; Gallacher, May, Montori, & Mair, 2011; Jani et al., 2013), along with needing to practice important health behaviours, such as maintaining a healthy diet and physical activity. These demands may limit their ability to engage in cognitive intervention programmes. Moreover, motivation to engage in such programme may be further complicated by mental health disorders, especially depression and anxiety disorders (Clarke & Currie, 2009; Katon, Lin, & Kroenke, 2007).

Second, it is likely the enrichment population included primarily highly motivated subjects, thus it is unclear whether our results would generalise to less motivated subjects. Troyer et al. (2008) reported that the number of sessions attended and at-home assignments completed by the participant positively predicted the observed changes in memory. Thus, suggesting that the individual's motivation plays a crucial role in cognitive intervention. Furthermore, the lack of motivation or apathy has been suggested to correlate with greater memory impairment and predicted the progression to dementia (Robert et al., 2008). This thus creates a paradox for intervention studies, in that ideally intervention studies would want to capture these individuals as they may be at higher risk than the general elderly population. However, these individuals are less likely to respond to participant requests in advertisements and even when they do respond they are less likely to carry through and complete such programme. Future studies would benefit from careful analysis of potential biases in the recruitment and retention of study participants.

8.2.4 *Follow-Up*

One issue concerns the long-term, disease modifying effects of the Cognitive Enrichment Programme. Due to time constraints, we only examined the immediate short-term effects of enrichment in MCI. Future studies should also include follow-up sessions to ascertain any maintenance effects and rate of conversion to AD. Evidence of long-term maintenance of benefits in MCI due to intervention is crucial given the neurodegenerative

nature of the condition. A delay of symptom progression and conversion to dementia should be considered as an ultimate efficacy outcome.

8.2.5 *Concluding Remarks and Future Direction*

Despite these limitations, this study represents the first attempt to evaluate a novel cognitive enrichment programme designed to enhance DMN activity and connectivity, and therefore cognition in elderly with MCI, who are a vulnerable group with high risk of developing dementia. Our preliminary results provided support for the feasibility of this type of intervention programme in MCI. For example, we did not know in advance whether older adults with MCI and their partner would be willing and able to commit to an intervention programme over a 4-6-month period. Furthermore, we demonstrated that cognitive enrichment is associated with positive effects on DMN connectivity at rest. However, results from the present study must be interpreted with great care due to the small sample size. The next step would be to boost the current sample size up either with the waitlist group, or to replicate the study with a larger sample size. It is important for future studies to evaluate the long-term benefits and real-world generalisation of such intervention programme. Furthermore, the present study had a particular emphasis on the changes in the functional integration of the DMN in patients with MCI. A recent study indicated that AD is associated with an alteration of large-scale functional brain networks that extend beyond the DMN (He et al., 2014; R. Li et al., 2012; Weiler et al., 2014; Zhang et al., 2015). Thus, it would be useful for future studies to examine whether the

Cognitive Enrichment Programme show beneficial effects on other brain networks in patients with MCI.

CHAPTER 9 - References

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CHAPTER 10 - Appendices

10.1 **Appendix A – Descriptions of Standardised Neuropsychological Tests Used**

10.1.1 *Pre-Morbid Intelligence*

The Test of Premorbid Functioning (TOFP; Pearson, 2009) provides an estimate of an individual's level of intellectual functioning before the onset of injury or illness. It involves asking the participants to read out loud a list of 70 words that have atypical grapheme to phoneme translations. The total score is the number of words read correctly.

10.1.2 *Activities of Daily Living*

In the current study, participants' ability to perform activities of daily living was evaluated through the Clinical Dementia Rating (CDR). The CDR is a semi-structured interview with the participants and informants. It consists of six domains of functioning: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care of the participant. Each domain is rated on a five-point scale: CDR 0 = no cognitive impairment, CDR 0.5 = very mild dementia, CDR 1 = mild, CDR 2 = moderate, and CDR 3 = severe. In this study, the global CDR score was computed using the Washington University online algorithm (<http://www.biostat.wustl.edu/intrnet/broker>). MCI participants had a global CDR of 0 or

0.5, participants with a CDR score ≥ 1 were classified as demented and excluded from the cognitive enrichment study.

10.1.3 *Global Cognitive Functioning*

General cognitive status was assessed with the use of the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog; Graham, Cully, Snow, Massman, & Doody, 2004) and the Dementia Rating Scale-2 (DRS-2; Jurica, Leitten, & Mattis, 2001).

The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) is a brief screening test that was developed specifically for the detection of MCI. It assesses a number of different cognitive domains, including attention and concentration, executive function, memory, language, visuospatial abilities, working memory, and orientation. To adjust for education levels, one point is added for participants with 12 years or fewer of formal education, for a possible maximum score of 30 points. A final total score of 26 and above is considered normal.

The modified version of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog; Mohs et al., 1997) was used. The ADAS-modified version consists of 13 tasks, including 9 performance-based assessments and 4 rater-based items. The performance items include word recall, following commands, constructional praxis,

naming, ideational praxis, orientation, delayed recall, word recognition, and number cancellation. The rater-based items include remembering test items, comprehension, word finding ability, and spoken language ability. The total score has a range of 0 to 85, higher scores indicated greater severity.

The Dementia Rating Scale -2 (DRS-2; Jurica et al., 2001) was constructed to assess cognitive abilities in dementia patients, differentiate levels of ability in these patients, and track their cognitive status over time. The scale provides a global measure of cognitive functioning as well as five subscales scores (attention, initiation/perseveration, construction, conceptualisation, and memory). A scaled score of 9 and above is described as ‘intact’, with scores between 6 and 8 described as mildly impaired, 4 to 5 as moderately impaired, and 3 or less as severely impaired (Jurica et al., 2001). In this study, the orientation items (date, month, year, day, place, and city) were crossed-scored with the MoCA, as both tests were completed within the same session.

10.1.4 *Attention and Processing Speed*

Attention and processing speed was assessed using the Digit Span Test (Wechsler, 2008a, 2008b), Stroop Colour Naming and Word Reading (Delis, Kaplan, & Kramer, 2001), and Trail Making Test-Part A (Mitrushina et al., 2005).

The Digit Span Test (Wechsler, 2008a, 2008b) measures auditory attention, immediate span of learning, and working memory. In this test, participants are asked to listen carefully to a series of random numbers, which are presented at a rate of one per second. The Digit Span is composed of three tasks: Digit Span Forward (DSF), Digit Span Backward (DSB), and Digit Span Sequencing (DSS). In the DSF, the participants are asked to repeat the numbers in a forward order, while in the DSB task, the numbers are recalled in reverse order. For the DSS task, the participants are required to recite the numbers in sequence starting with the lowest number.

The Stroop Colour Naming and Word Reading tests (Delis et al., 2001) require the participants to read aloud the colour/word as fast as they can. The Stroop Interference test is included under the executive function domain.

The Trail Making Test consists of two parts: A and B (Mitrushina et al., 2005). Part A examines visual scanning, numeric sequencing, and visuomotor speed, whereas Part B of the test involves more cognitive flexibility from the participants, hence it is included as part of the executive function domain. For Part A of the test, participants are asked to use a pencil to link together numbers presented in circles (1 to 25) in the ascending sequence. If the participant makes an error, the examiner is to correct them before the participant moves on to the next dot.

10.1.5 *Executive Function*

Executive function was assessed using the Verbal Fluency Test (Delis et al., 2001), Action Fluency Test (Piatt, Fields, Paolo, & Troster, 1999; Piatt et al., 2004), Trail Making Test-Part B (Mitrushina et al., 2005), Stroop Interference (Delis et al., 2001), Symbol Digit Modalities Test (A. Smith, 1982), and Design Fluency Test (Delis et al., 2001).

The Verbal Fluency Test (Delis et al., 2001) measures participants' ability to generate words, in response to a single letter and categorical stimuli, as well as generating words whilst alternating between two separate category stimuli. Participants are asked to name as many words as possible in 60 seconds.

The Action Fluency Test is a measure of verbal fluency in which participants are instructed to generate as many verbs (i.e., things that people do) as possible in 60 seconds (Piatt et al., 1999, 2004).

Part B of the Trail Making Test (Mitrushina et al., 2005) requires the participants to connect numbers and letters in an alternating numeric and alphabetic sequence (i.e., 1-A-2-B-3-C, etc) as fast as possible. The task is timed and the score represents the amount of time required to complete the task.

The Stroop Interference Test (Delis et al., 2001) requires the participant to name the colour of the ink in which the word was printed rather than read the actual word.

The Symbol Digit Modalities Test (SDMT; A. Smith, 1982) is a simple substitution task using a reference key with nine different digit-symbol pairs. It captures divided attention and processing speed. Each participant was given 90 seconds to pair specific numbers with given abstract symbols.

The Design Fluency Test (Delis et al., 2001) consists of three conditions in which participants are required to create as many novel designs as possible within one minute by connecting the dots using four straight lines. The three conditions are referred to as filled dots (connecting filled dots), empty dots (connecting empty dots while filled dots function as distractors), and switching (alternating between connecting filled and empty dots).

10.1.6 *Visuospatial Function*

Visuospatial function was assessed using the Silhouettes (Warrington & James, 1991), Judgement of Line Orientation (Benton et al., 1983), Matrix Reasoning (Wechsler, 2008a, 2008b), and Rey Complex Figure Test (Meyers & Meyers, 1995).

The Silhouettes, part of the Visual Object and Space Perception Battery (VOSP; Warrington & James, 1991), consists of 15 silhouettes of animals and 15 of common objects, drawn from varying degrees of angular rotation. Participants are required to identify the drawings.

Judgement of Line Orientation (JLO; Benton et al., 1983) is a 30-item test of visuospatial perception. The JLO is presented in flip-book style where two lines appear at the top page, and a standard fan-shaped array of 11 lines appears at the bottom. Participants must identify the two lines from the bottom page that match the angles of the two lines of the top page.

Matrix Reasoning (Wechsler, 2008a, 2008b) involves participants viewing an incomplete matrix or series and select the response option that completes the matrix or series from a set of five alternatives.

The Rey Complex Figure Test (RCFT; Meyers & Meyers, 1995) evaluates visuospatial and constructional abilities and organisational strategy in the copy stage and visual memory in the recall stage. The copy trial involves participants drawing a complex geometric figure, there is minimal demand placed on memory during the copy condition. Whilst the participant is copying the drawing the examiner copies the participant's drawing using different coloured pens to capture organisational and sequential aspects of the participant's copy. The recall trials are included in the learning and memory domain.

10.1.7 *Learning and Memory*

Learning and memory was assessed using the California Verbal Learning Test – Second Edition (Delis et al., 2000), Rey Complex Figure Test (Meyers & Meyers, 1995), Brief Visuospatial Memory Test–Revised (Benedict, 1997), story recall from the Rivermead Behavioural Memory (B. A. Wilson, Cockburn, & Baddeley, 2003; B. A. Wilson et al., 2008), Rappel Indice 48 Items (Adam et al., 2007), and Visual Association Test (Lindeboom & Schmand, 2003; Lindeboom et al., 2002).

The Short Form of the California Verbal Learning Test – Second Edition (CVLT-II SF) measures participant's ability to learn and recall a list of nine words, the words are taken from three semantic categories (Delis et al., 2000). The word list is orally administered to the participants over four acquisition trails. Participants are asked to recall those words after a short delay of counting backwards from 100 for 30 seconds. The long-delay free recall is administered after a 10-minute delay filled with non-verbal tasks.

The short-delay recall of the Rey Complex Figure Test (RCFT; Meyers & Meyers, 1995) requires the participants to recall and reproduce the figure and is administered after a 3-minute interval filled with a short conversation. The participants are asked to reproduce the complex figure again after a further 30-minute delay.

The Brief Visuospatial Memory Test–Revised (BVMT-R; Benedict, 1997) consists of six geometric designs on an A4 size page. The page is shown to the participants for 10 seconds. There are three acquisition trials, and participants are asked to reproduce the designs immediately after each trial. Approximately 25 minutes following the acquisition trials, participants are again asked to reproduce the designs.

In the Story Recall subtest from the Rivermead Behavioural Memory Test (B. A. Wilson et al., 2003; B. A. Wilson et al., 2008), a brief fact-laden passage is read to the participants and they are asked to memorise it for immediate recall and recall in 20 minutes. The story from the RBMT-second edition was used at baseline assessment, while the RBMT-third edition was used at the start and end of the enrichment programme.

The Rappel Indice 48 Items (RI-48 Task; Adam et al., 2007) is a simplified and shortened form of the original selective reminding test developed by Buschke (1997). It comprises of 48 items belonging to 12 different semantic categories. The items are presented to participants as written words on 12 consecutive cards, each card containing four items with each item from a different category. Participants are asked to identify and encode each item when its category is presented by the examiner. The card is then removed from the participant, and immediate cued recall is performed for these four words. If participants are unable to give an item in response to its category, the card is presented again and the procedure of identification and cued recall is repeated for this

item alone. Once the immediate cued recall for a card is completed, the next card with four new items is presented and encoded in the same way. After the recall of the last card, participants are asked to count backward for 20 seconds. Participants are then asked to recall the four items from each category.

The Visual Association Test (VAT; Lindeboom & Schmand, 2003; Lindeboom et al., 2002) consists of six cue cards showing only one of the objects (cue) and six association cards showing two interacting objects (cue and target). The participants are asked to name the objects on the cue cards and then the pairs of interacting objects on the association cards. Immediately after naming, the person is presented with the cue cards again and is asked to recall the corresponding targets.

10.1.8 *Language*

The language domain was assessed using the Boston Naming Test (Lansing et al., 1999) and Indiana University Token Test (Unverzagt et al., 1999).

The Boston Naming Test (BNT) measures participants' ability to name objects following visual representations of the objects. The current study used the 15-item version, which has been shown to be comparable to the 60-item version in discriminating between AD and healthy controls (Lansing et al., 1999).

In the Indiana University Token Test (Unverzagt et al., 1999), participants are presented with an A4 size sheet of paper, with an array of 16 items, that varied in shape (circle and squares), colour (red, black, yellow, and green), and size (large and small). Participants are read a series of 12 commands graded in complexity. Items passed on the first try are awarded two points, and items passed on the second try are awarded one point.

10.2 Appendix B – Cross-Tabulation Tables for Confirmed MCI vs. Non-MCI

Table 10-1

Confirmed MCI vs. Non-MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 15

[illegible]

Note. Confirmed MCI; F = non-MCI. z-score ranges from +3 to -3.

Table 10-2
Confirmed MCI vs. Non-MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 16

[illegible]

Note. Confirmed MCI; F = non-MCI. z-score ranges from +3 to -3.

Table 10-8
Confirmed MCI vs. Non-MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 22

[illegible]

Note. Confirmed MCI; F = non-MCI. z-score ranges from +3 to -3.

Confirmed MCI vs. Non-MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 26

Rey Complex Figure Copy

Note. Confirmed MCI; F = non-MCI. z-score ranges from +3 to -3.

Confirmed MCI vs. Non-MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 28

Rey Complex Figure Copy

Note. Confirmed MCI; F = non-MCI. z-score ranges from +3 to -3.

Table 10-15

Confirmed MCI vs. Non-MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 29

	Rey Complex Figure Recall																								
	-3	-2.9	-2.8	-2.7	-2.6	-2.5	-2.4	-2.3	-2.2	-2.1	-2	-1.9	-1.8	-1.7	-1.6	-1.5	-1.4	-1.3	-1.2	-1.1	-1	-0.9	-0.8	>-0.7	
Rey Complex Figure Copy	-3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	
	-2.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	
	-2.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	
	-2.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	
	-2.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	
	-2.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	
	-2.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	
	-2.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	
	-2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	
	-1.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	
	-1.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-1.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-1.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-1.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-1.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-1.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-1.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-1.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-0.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-0.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-0.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-0.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-0.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-0.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-0.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-0.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	-0.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
	0	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	
0.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F		
0.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F		
0.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F		
0.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F		
0.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F		
0.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F		
0.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F		
0.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F		
0.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F		
1	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.1	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.2	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.3	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.4	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.5	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.6	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.7	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.8	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.9	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.1	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.2	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.3	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.4	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.5	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.6	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.7	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.8	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.9	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
3	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		

Note. Confirmed MCI; F = non-MCI. z-score ranges from +3 to -3.

Table 10-16

Confirmed MCI vs. Non-MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 30

	Rey Complex Figure Recall																					
	-3	-2.9	-2.8	-2.7	-2.6	-2.5	-2.4	-2.3	-2.2	-2.1	-2	-1.9	-1.8	-1.7	-1.6	-1.5	-1.4	-1.3	-1.2	-1.1	>-1	
Rey Complex Figure Copy	-3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
0	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F		
0.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F		
0.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F		
0.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F		
0.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F		
0.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F		
0.6	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
0.7	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
0.8	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
0.9	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.1	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.2	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.3	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.4	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.5	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.6	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.7	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.8	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
1.9	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.1	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.2	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.3	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.4	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.5	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.6	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.7	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.8	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
2.9	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		
3	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		

Note. Confirmed MCI; F = non-MCI. z-score ranges from +3 to -3.

10.3 Appendix C – Cross-Tabulation Tables for Confirmed MCI vs. Probable HC

Table 10-17

Confirmed MCI vs. Probable HC: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 15

Key Complex Figure Copy	Key Complex Figure Recall																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																			
	<-1.2	-1.1	-1	-0.9	-0.8	-0.7	-0.6	-0.5	-0.4	-0.3	-0.2	-0.1	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2	2.1	>2.2																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																	
	-3	-2.9	-2.8	-2.7	-2.6	-2.5	-2.4	-2.3	-2.2	-2.1	-2	-1.9	-1.8	-1.7	-1.6	-1.5	-1.4	-1.3	-1.2	-1.1	-1	-0.9	-0.8	-0.7	-0.6	-0.5	-0.4	-0.3	-0.2	-0.1	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2	2.1	>2.2																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																															
	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T

Note. Confirmed MCI; F = Probable HC. z-score ranges from +3 to -3.

Confirmed MCI vs. Probable HC: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 16

Note. Confirmed MCI; F = Probable HC. z-score ranges from +3 to -3.

Confirmed MCI vs. Probable HC: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 18

Note. Confirmed MCI; F = Probable HC. z-score ranges from +3 to -3.

Confirmed MCI vs. Probable HC: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 21

Note. Confirmed MCI; F = Probable HC. z-score ranges from +3 to -3.

Confirmed MCI vs. Probable HC: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 23

Note. Confirmed MCI; F = Probable HC. z-score ranges from +3 to -3.

Confirmed MCI vs. Probable HC: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 25

Note. Confirmed MCI; F = Probable HC. z-score ranges from +3 to -3.

Confirmed MCI vs. Probable HC: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 26

Key Complex Figure Copy

Note. Confirmed MCI; F = Probable HC. z-score ranges from +3 to -3.

Confirmed MCI vs. Probable HC: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 27

Rey Complex Figure Copy

Note. Confirmed MCI; F = Probable HC. z-score ranges from +3 to -3.

Confirmed MCI vs. Probable HC: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 28

Rey Complex Figure Copy

Note. Confirmed MCI; F = Probable HC. z-score ranges from +3 to -3.

Confirmed MCI vs. Probable HC: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 29

Rey Complex Figure Copy

Note. Confirmed MCI; F = Probable HC. z-score ranges from +3 to -3.

Table 10-32

Confirmed MCI vs. Probable HC: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 30

	Rey Complex Figure Recall																										
	-3	-2.9	-2.8	-2.7	-2.6	-2.5	-2.4	-2.3	-2.2	-2.1	-2	-1.9	-1.8	-1.7	-1.6	-1.5	-1.4	-1.3	-1.2	-1.1	-1	-0.9	-0.8	-0.7	-0.6	>-0.5	
Rey Complex Figure Copy	-3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F
	-2.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F
	-2.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F
	-2.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F
	-2.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F
	-2.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F
	-2.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F
	-2.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F
	-2.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F
	-2.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F
	-2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F
	-1.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F
	-1.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F
	-1.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F
	-1.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F
	-1.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F
	-1.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-1.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F
	-1.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F
	-1.1	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F
	-1	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.9	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.8	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.7	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.6	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.5	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.4	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.3	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.2	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.1	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
0	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.1	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.2	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.3	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.4	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.5	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.6	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.7	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.8	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.9	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.1	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.2	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.3	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.4	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.5	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.6	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.7	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.8	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.9	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.1	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.2	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.3	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.4	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.5	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.6	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.7	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.8	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.9	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
3	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	

Note. Confirmed MCI; F = Probable HC. z-score ranges from +3 to -3.

10.4 Appendix D – Cross-Tabulation Tables for Confirmed MCI vs. Possible MCI

Table 10-33

Confirmed MCI vs. Possible MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 15

[illegible]

Note. T = Confirmed MCI; F = Possible MCI. z-score ranges from +3 to -3.

Confirmed MCI vs. Possible MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 17

Note. T = Confirmed MCI; F = Possible MCI. z-score ranges from +3 to -3.

Confirmed MCI vs. Possible MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 18

Note. T = Confirmed MCI; F = Possible MCI. z-score ranges from +3 to -3.

Table 10-41

Confirmed MCI vs. Possible MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 23

	Rey Complex Figure Recall																										
	-3	-2.9	-2.8	-2.7	-2.6	-2.5	-2.4	-2.3	-2.2	-2.1	-2	-1.9	-1.8	-1.7	-1.6	-1.5	-1.4	-1.3	-1.2	-1.1	-1	-0.9	-0.8	-0.7	-0.6	-0.5	>-0.4
Rey Complex Figure Copy	-3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F
	-2.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F
	-2.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F
	-2.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F
	-2.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F
	-2.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F
	-2.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F
	-2.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F
	-2.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F
	-2.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F
	-2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F
	-1.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F
	-1.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F
	-1.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F
	-1.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F
	-1.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F
	-1.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F
	-1.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F
	-1.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F
	-1.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F
	-1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F
	-0.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-0.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F
	-0.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F
	-0.6	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.5	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.4	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.3	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.2	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.1	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	0	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
0.1	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.2	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.3	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.4	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.5	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.6	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.7	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.8	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.9	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.1	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.2	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.3	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.4	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.5	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.6	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.7	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.8	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.9	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.1	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.2	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.3	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.4	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.5	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.6	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.7	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.8	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.9	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
3	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	

Note. T = Confirmed MCI; F = Possible MCI. z-score ranges from +3 to -3.

Table 10-42

Confirmed MCI vs. Possible MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 24

	Rey Complex Figure Recall																									
	-3	-2.9	-2.8	-2.7	-2.6	-2.5	-2.4	-2.3	-2.2	-2.1	-2	-1.9	-1.8	-1.7	-1.6	-1.5	-1.4	-1.3	-1.2	-1.1	-1	-0.9	-0.8	-0.7	>-0.6	
Rey Complex Figure Copy	-3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	-0.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	0	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	0.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	0.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	0.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	0.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	0.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	0.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	0.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	0.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	0.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	1.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	1.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	1.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	1.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	1.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	1.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	1.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	1.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	1.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	2.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	2.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	2.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	2.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	2.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	2.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	2.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	2.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	2.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	
	3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	

Note. T = Confirmed MCI; F = Possible MCI. z-score ranges from +3 to -3.

Table 10-43

Confirmed MCI vs. Possible MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 25

	Rey Complex Figure Recall																					
	-3	-2.9	-2.8	-2.7	-2.6	-2.5	-2.4	-2.3	-2.2	-2.1	-2	-1.9	-1.8	-1.7	-1.6	-1.5	-1.4	-1.3	-1.2	-1.1	-1	>-0.9
Rey Complex Figure Copy	-3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F
	-2.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F
	-2.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F
	-2.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F
	-2.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F
	-2.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F
	-2.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F
	-2.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F
	-2.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F
	-2.1	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F
	-2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F
	-1.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F
	-1.8	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F
	-1.7	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F
	-1.6	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F
	-1.5	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F
	-1.4	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F
	-1.3	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F
	-1.2	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-1.1	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-1	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-0.9	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-0.8	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-0.7	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-0.6	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-0.5	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-0.4	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-0.3	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-0.2	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-0.1	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	0	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	0.1	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	0.2	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	0.3	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	0.4	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	0.5	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	0.6	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	0.7	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	0.8	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	0.9	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	1	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	1.1	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	1.2	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	1.3	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	1.4	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	1.5	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	1.6	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	1.7	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	1.8	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	1.9	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	2	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	2.1	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	2.2	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	2.3	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	2.4	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	2.5	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	2.6	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	2.7	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	2.8	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	2.9	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	3	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F

Note. T = Confirmed MCI; F = Possible MCI. z-score ranges from +3 to -3.

Table 10-44

Confirmed MCI vs. Possible MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 26

	Rey Complex Figure Recall																		
	-3	-2.9	-2.8	-2.7	-2.6	-2.5	-2.4	-2.3	-2.2	-2.1	-2	-1.9	-1.8	-1.7	-1.6	-1.5	-1.4	-1.3	>-1.2
Rey Complex Figure Copy	-3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F
	-2.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F
	-2.8	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F
	-2.7	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F
	-2.6	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F
	-2.5	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F
	-2.4	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F
	-2.3	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F
	-2.2	T	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F
	-2.1	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F
	-2	T	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F
	-1.9	T	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F
	-1.8	T	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F
	-1.7	T	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F
	-1.6	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F
	-1.5	T	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F
	-1.4	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F
	-1.3	T	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F
	-1.2	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-1.1	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-1	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-0.9	T	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-0.8	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F
	-0.7	T	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F
	-0.6	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.5	T	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.4	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.3	T	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.2	T	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.1	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
0	T	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.1	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.2	T	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.3	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.4	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.5	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.6	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.7	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.8	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
0.9	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.1	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.2	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.3	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.4	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.5	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.6	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.7	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.8	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
1.9	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.1	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.2	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.3	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.4	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.5	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.6	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.7	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.8	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
2.9	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
3	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	

Note. T = Confirmed MCI; F = Possible MCI. z-score ranges from +3 to -3.

Table 10-45

Confirmed MCI vs. Possible MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 27

	Rey Complex Figure Recall														
	-3	-2.9	-2.8	-2.7	-2.6	-2.5	-2.4	-2.3	-2.2	-2.1	-2	-1.9	-1.8	-1.7	-1.6
Rey Complex Figure Copy	-3	T	T	T	T	T	T	T	T	T	T	T	T	T	T
	-2.9	T	T	T	T	T	T	T	T	T	T	T	T	T	T
	-2.8	T	T	T	T	T	T	T	T	T	T	T	T	T	F
	-2.7	T	T	T	T	T	T	T	T	T	T	T	T	T	F
	-2.6	T	T	T	T	T	T	T	T	T	T	T	T	F	F
	-2.5	T	T	T	T	T	T	T	T	T	T	T	T	F	F
	-2.4	T	T	T	T	T	T	T	T	T	T	T	F	F	F
	-2.3	T	T	T	T	T	T	T	T	T	T	F	F	F	F
	-2.2	T	T	T	T	T	T	T	T	T	T	F	F	F	F
	-2.1	T	T	T	T	T	T	T	T	T	F	F	F	F	F
	-2	T	T	T	T	T	T	T	T	F	F	F	F	F	F
	-1.9	T	T	T	T	T	T	T	T	F	F	F	F	F	F
	-1.8	T	T	T	T	T	T	T	T	F	F	F	F	F	F
	-1.7	T	T	T	T	T	T	T	T	F	F	F	F	F	F
	-1.6	T	T	T	T	T	T	T	F	F	F	F	F	F	F
	-1.5	T	T	T	T	T	T	T	F	F	F	F	F	F	F
	-1.4	T	T	T	T	T	T	F	F	F	F	F	F	F	F
	-1.3	T	T	T	T	T	F	F	F	F	F	F	F	F	F
	-1.2	T	T	T	T	T	F	F	F	F	F	F	F	F	F
	-1.1	T	T	T	T	T	F	F	F	F	F	F	F	F	F
	-1	T	T	T	T	F	F	F	F	F	F	F	F	F	F
	-0.9	T	T	T	T	F	F	F	F	F	F	F	F	F	F
	-0.8	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-0.7	T	T	T	F	F	F	F	F	F	F	F	F	F	F
	-0.6	T	T	F	F	F	F	F	F	F	F	F	F	F	F
	-0.5	T	T	F	F	F	F	F	F	F	F	F	F	F	F
	-0.4	T	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.3	T	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.2	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	-0.1	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	0	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	0.1	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	0.2	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	0.3	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	0.4	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	0.5	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	0.6	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	0.7	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	0.8	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	0.9	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	1	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	1.1	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	1.2	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	1.3	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	1.4	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	1.5	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	1.6	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	1.7	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	1.8	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	1.9	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	2	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	2.1	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	2.2	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	2.3	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	2.4	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	2.5	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	2.6	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	2.7	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	2.8	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	2.9	F	F	F	F	F	F	F	F	F	F	F	F	F	F
	3	F	F	F	F	F	F	F	F	F	F	F	F	F	F

Note. T = Confirmed MCI; F = Possible MCI. z-score ranges from +3 to -3.

Table 10-46

Confirmed MCI vs. Possible MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 28

	Rey Complex Figure Recall												
	-3	-2.9	-2.8	-2.7	-2.6	-2.5	-2.4	-2.3	-2.2	-2.1	-2	-1.9	>-1.8
Rey Complex Figure Copy													
-3	T	T	T	T	T	T	T	T	T	T	T	T	F
-2.9	T	T	T	T	T	T	T	T	T	T	T	T	F
-2.8	T	T	T	T	T	T	T	T	T	T	T	F	F
-2.7	T	T	T	T	T	T	T	T	T	T	T	F	F
-2.6	T	T	T	T	T	T	T	T	T	T	F	F	F
-2.5	T	T	T	T	T	T	T	T	T	T	F	F	F
-2.4	T	T	T	T	T	T	T	T	T	F	F	F	F
-2.3	T	T	T	T	T	T	T	T	F	F	F	F	F
-2.2	T	T	T	T	T	T	T	T	F	F	F	F	F
-2.1	T	T	T	T	T	T	T	T	F	F	F	F	F
-2	T	T	T	T	T	T	T	F	F	F	F	F	F
-1.9	T	T	T	T	T	T	T	F	F	F	F	F	F
-1.8	T	T	T	T	T	T	F	F	F	F	F	F	F
-1.7	T	T	T	T	T	F	F	F	F	F	F	F	F
-1.6	T	T	T	T	T	F	F	F	F	F	F	F	F
-1.5	T	T	T	T	F	F	F	F	F	F	F	F	F
-1.4	T	T	T	T	F	F	F	F	F	F	F	F	F
-1.3	T	T	T	F	F	F	F	F	F	F	F	F	F
-1.2	T	T	T	F	F	F	F	F	F	F	F	F	F
-1.1	T	T	F	F	F	F	F	F	F	F	F	F	F
-1	T	T	F	F	F	F	F	F	F	F	F	F	F
-0.9	T	F	F	F	F	F	F	F	F	F	F	F	F
-0.8	T	F	F	F	F	F	F	F	F	F	F	F	F
-0.7	F	F	F	F	F	F	F	F	F	F	F	F	F
-0.6	F	F	F	F	F	F	F	F	F	F	F	F	F
-0.5	F	F	F	F	F	F	F	F	F	F	F	F	F
-0.4	F	F	F	F	F	F	F	F	F	F	F	F	F
-0.3	F	F	F	F	F	F	F	F	F	F	F	F	F
-0.2	F	F	F	F	F	F	F	F	F	F	F	F	F
-0.1	F	F	F	F	F	F	F	F	F	F	F	F	F
0	F	F	F	F	F	F	F	F	F	F	F	F	F
0.1	F	F	F	F	F	F	F	F	F	F	F	F	F
0.2	F	F	F	F	F	F	F	F	F	F	F	F	F
0.3	F	F	F	F	F	F	F	F	F	F	F	F	F
0.4	F	F	F	F	F	F	F	F	F	F	F	F	F
0.5	F	F	F	F	F	F	F	F	F	F	F	F	F
0.6	F	F	F	F	F	F	F	F	F	F	F	F	F
0.7	F	F	F	F	F	F	F	F	F	F	F	F	F
0.8	F	F	F	F	F	F	F	F	F	F	F	F	F
0.9	F	F	F	F	F	F	F	F	F	F	F	F	F
1	F	F	F	F	F	F	F	F	F	F	F	F	F
1.1	F	F	F	F	F	F	F	F	F	F	F	F	F
1.2	F	F	F	F	F	F	F	F	F	F	F	F	F
1.3	F	F	F	F	F	F	F	F	F	F	F	F	F
1.4	F	F	F	F	F	F	F	F	F	F	F	F	F
1.5	F	F	F	F	F	F	F	F	F	F	F	F	F
1.6	F	F	F	F	F	F	F	F	F	F	F	F	F
1.7	F	F	F	F	F	F	F	F	F	F	F	F	F
1.8	F	F	F	F	F	F	F	F	F	F	F	F	F
1.9	F	F	F	F	F	F	F	F	F	F	F	F	F
2	F	F	F	F	F	F	F	F	F	F	F	F	F
2.1	F	F	F	F	F	F	F	F	F	F	F	F	F
2.2	F	F	F	F	F	F	F	F	F	F	F	F	F
2.3	F	F	F	F	F	F	F	F	F	F	F	F	F
2.4	F	F	F	F	F	F	F	F	F	F	F	F	F
2.5	F	F	F	F	F	F	F	F	F	F	F	F	F
2.6	F	F	F	F	F	F	F	F	F	F	F	F	F
2.7	F	F	F	F	F	F	F	F	F	F	F	F	F
2.8	F	F	F	F	F	F	F	F	F	F	F	F	F
2.9	F	F	F	F	F	F	F	F	F	F	F	F	F
3	F	F	F	F	F	F	F	F	F	F	F	F	F

Note. T = Confirmed MCI; F = Possible MCI. z-score ranges from +3 to -3.

Table 10-47

Confirmed MCI vs. Possible MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 29

	Rey Complex Figure Recall										
	-3	-2.9	-2.8	-2.7	-2.6	-2.5	-2.4	-2.3	-2.2	-2.1	>-2
Rey Complex Figure Copy											
-3	T	T	T	T	T	T	T	T	T	T	F
-2.9	T	T	T	T	T	T	T	T	T	T	F
-2.8	T	T	T	T	T	T	T	T	T	F	F
-2.7	T	T	T	T	T	T	T	T	F	F	F
-2.6	T	T	T	T	T	T	T	T	F	F	F
-2.5	T	T	T	T	T	T	T	F	F	F	F
-2.4	T	T	T	T	T	T	F	F	F	F	F
-2.3	T	T	T	T	T	T	F	F	F	F	F
-2.2	T	T	T	T	T	F	F	F	F	F	F
-2.1	T	T	T	T	T	F	F	F	F	F	F
-2	T	T	T	T	F	F	F	F	F	F	F
-1.9	T	T	T	T	F	F	F	F	F	F	F
-1.8	T	T	T	F	F	F	F	F	F	F	F
-1.7	T	T	T	F	F	F	F	F	F	F	F
-1.6	T	T	F	F	F	F	F	F	F	F	F
-1.5	T	T	F	F	F	F	F	F	F	F	F
-1.4	T	F	F	F	F	F	F	F	F	F	F
-1.3	T	F	F	F	F	F	F	F	F	F	F
-1.2	F	F	F	F	F	F	F	F	F	F	F
-1.1	F	F	F	F	F	F	F	F	F	F	F
-1	F	F	F	F	F	F	F	F	F	F	F
-0.9	F	F	F	F	F	F	F	F	F	F	F
-0.8	F	F	F	F	F	F	F	F	F	F	F
-0.7	F	F	F	F	F	F	F	F	F	F	F
-0.6	F	F	F	F	F	F	F	F	F	F	F
-0.5	F	F	F	F	F	F	F	F	F	F	F
-0.4	F	F	F	F	F	F	F	F	F	F	F
-0.3	F	F	F	F	F	F	F	F	F	F	F
-0.2	F	F	F	F	F	F	F	F	F	F	F
-0.1	F	F	F	F	F	F	F	F	F	F	F
0	F	F	F	F	F	F	F	F	F	F	F
0.1	F	F	F	F	F	F	F	F	F	F	F
0.2	F	F	F	F	F	F	F	F	F	F	F
0.3	F	F	F	F	F	F	F	F	F	F	F
0.4	F	F	F	F	F	F	F	F	F	F	F
0.5	F	F	F	F	F	F	F	F	F	F	F
0.6	F	F	F	F	F	F	F	F	F	F	F
0.7	F	F	F	F	F	F	F	F	F	F	F
0.8	F	F	F	F	F	F	F	F	F	F	F
0.9	F	F	F	F	F	F	F	F	F	F	F
1	F	F	F	F	F	F	F	F	F	F	F
1.1	F	F	F	F	F	F	F	F	F	F	F
1.2	F	F	F	F	F	F	F	F	F	F	F
1.3	F	F	F	F	F	F	F	F	F	F	F
1.4	F	F	F	F	F	F	F	F	F	F	F
1.5	F	F	F	F	F	F	F	F	F	F	F
1.6	F	F	F	F	F	F	F	F	F	F	F
1.7	F	F	F	F	F	F	F	F	F	F	F
1.8	F	F	F	F	F	F	F	F	F	F	F
1.9	F	F	F	F	F	F	F	F	F	F	F
2	F	F	F	F	F	F	F	F	F	F	F
2.1	F	F	F	F	F	F	F	F	F	F	F
2.2	F	F	F	F	F	F	F	F	F	F	F
2.3	F	F	F	F	F	F	F	F	F	F	F
2.4	F	F	F	F	F	F	F	F	F	F	F
2.5	F	F	F	F	F	F	F	F	F	F	F
2.6	F	F	F	F	F	F	F	F	F	F	F
2.7	F	F	F	F	F	F	F	F	F	F	F
2.8	F	F	F	F	F	F	F	F	F	F	F
2.9	F	F	F	F	F	F	F	F	F	F	F
3	F	F	F	F	F	F	F	F	F	F	F

Note. T = Confirmed MCI; F = Possible MCI. z-score ranges from +3 to -3.

Table 10-48

Confirmed MCI vs. Possible MCI: Cut-Off Scores for RCFT Copy and RCFT Recall when MoCA Score of 30

	Rey Complex Figure Recall							
	-3	-2.9	-2.8	-2.7	-2.6	-2.5	-2.4	>-2.3
Rey Complex Figure Copy	-3	T	T	T	T	T	T	F
	-2.9	T	T	T	T	T	T	F
	-2.8	T	T	T	T	T	T	F
	-2.7	T	T	T	T	T	F	F
	-2.6	T	T	T	T	T	F	F
	-2.5	T	T	T	T	F	F	F
	-2.4	T	T	T	T	F	F	F
	-2.3	T	T	T	F	F	F	F
	-2.2	T	T	T	F	F	F	F
	-2.1	T	T	F	F	F	F	F
	-2	T	T	F	F	F	F	F
	-1.9	T	F	F	F	F	F	F
	-1.8	F	F	F	F	F	F	F
	-1.7	F	F	F	F	F	F	F
	-1.6	F	F	F	F	F	F	F
	-1.5	F	F	F	F	F	F	F
	-1.4	F	F	F	F	F	F	F
	-1.3	F	F	F	F	F	F	F
	-1.2	F	F	F	F	F	F	F
	-1.1	F	F	F	F	F	F	F
	-1	F	F	F	F	F	F	F
	-0.9	F	F	F	F	F	F	F
	-0.8	F	F	F	F	F	F	F
	-0.7	F	F	F	F	F	F	F
	-0.6	F	F	F	F	F	F	F
	-0.5	F	F	F	F	F	F	F
	-0.4	F	F	F	F	F	F	F
	-0.3	F	F	F	F	F	F	F
	-0.2	F	F	F	F	F	F	F
	-0.1	F	F	F	F	F	F	F
	0	F	F	F	F	F	F	F
	0.1	F	F	F	F	F	F	F
	0.2	F	F	F	F	F	F	F
	0.3	F	F	F	F	F	F	F
	0.4	F	F	F	F	F	F	F
	0.5	F	F	F	F	F	F	F
	0.6	F	F	F	F	F	F	F
	0.7	F	F	F	F	F	F	F
	0.8	F	F	F	F	F	F	F
	0.9	F	F	F	F	F	F	F
	1	F	F	F	F	F	F	F
	1.1	F	F	F	F	F	F	F
	1.2	F	F	F	F	F	F	F
	1.3	F	F	F	F	F	F	F
	1.4	F	F	F	F	F	F	F
	1.5	F	F	F	F	F	F	F
	1.6	F	F	F	F	F	F	F
	1.7	F	F	F	F	F	F	F
	1.8	F	F	F	F	F	F	F
	1.9	F	F	F	F	F	F	F
	2	F	F	F	F	F	F	F
	2.1	F	F	F	F	F	F	F
	2.2	F	F	F	F	F	F	F
	2.3	F	F	F	F	F	F	F
	2.4	F	F	F	F	F	F	F
	2.5	F	F	F	F	F	F	F
	2.6	F	F	F	F	F	F	F
	2.7	F	F	F	F	F	F	F
	2.8	F	F	F	F	F	F	F
	2.9	F	F	F	F	F	F	F
	3	F	F	F	F	F	F	F

Note. T = Confirmed MCI; F = Possible MCI. z-score ranges from +3 to -3.

10.5 Appendix E – Instructions for Task fMRI

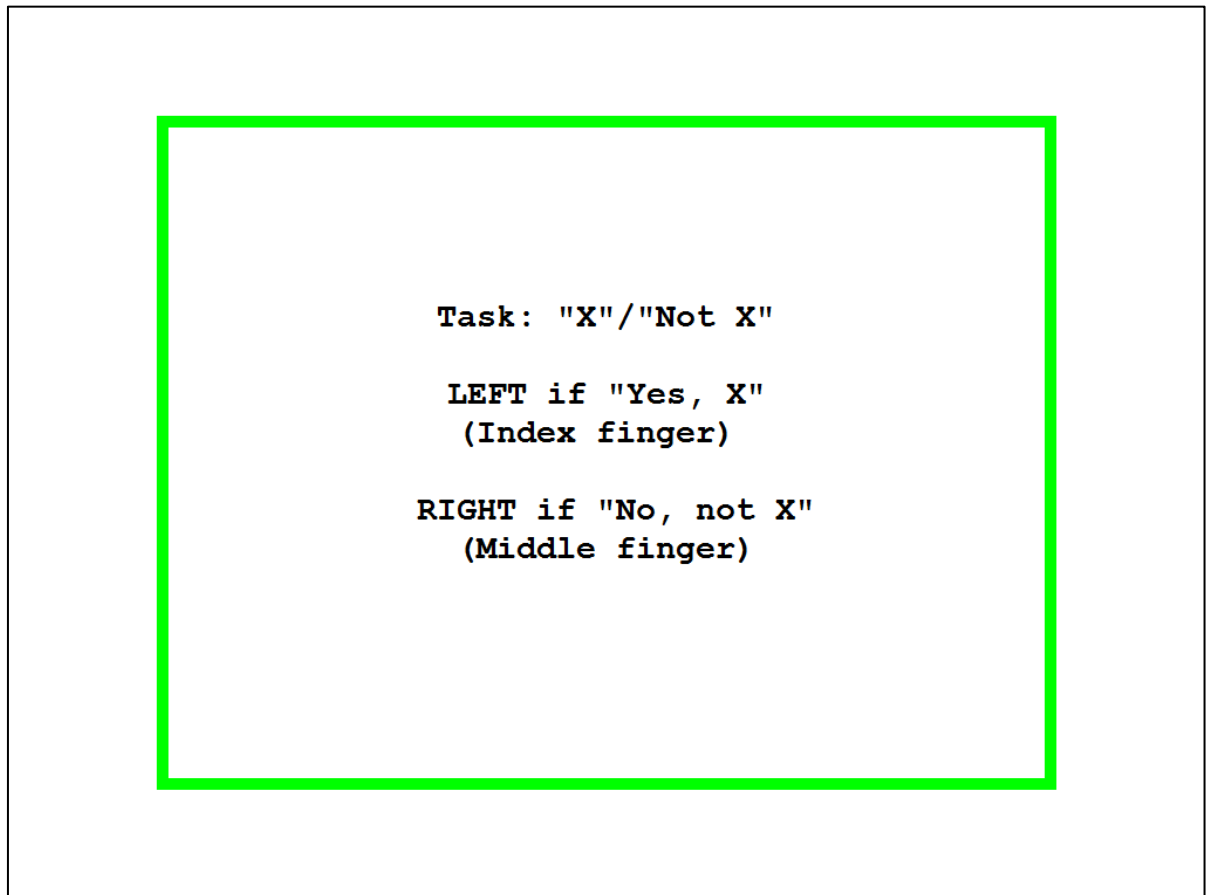


Figure 10-1. Instruction screen for the x-not-x task.

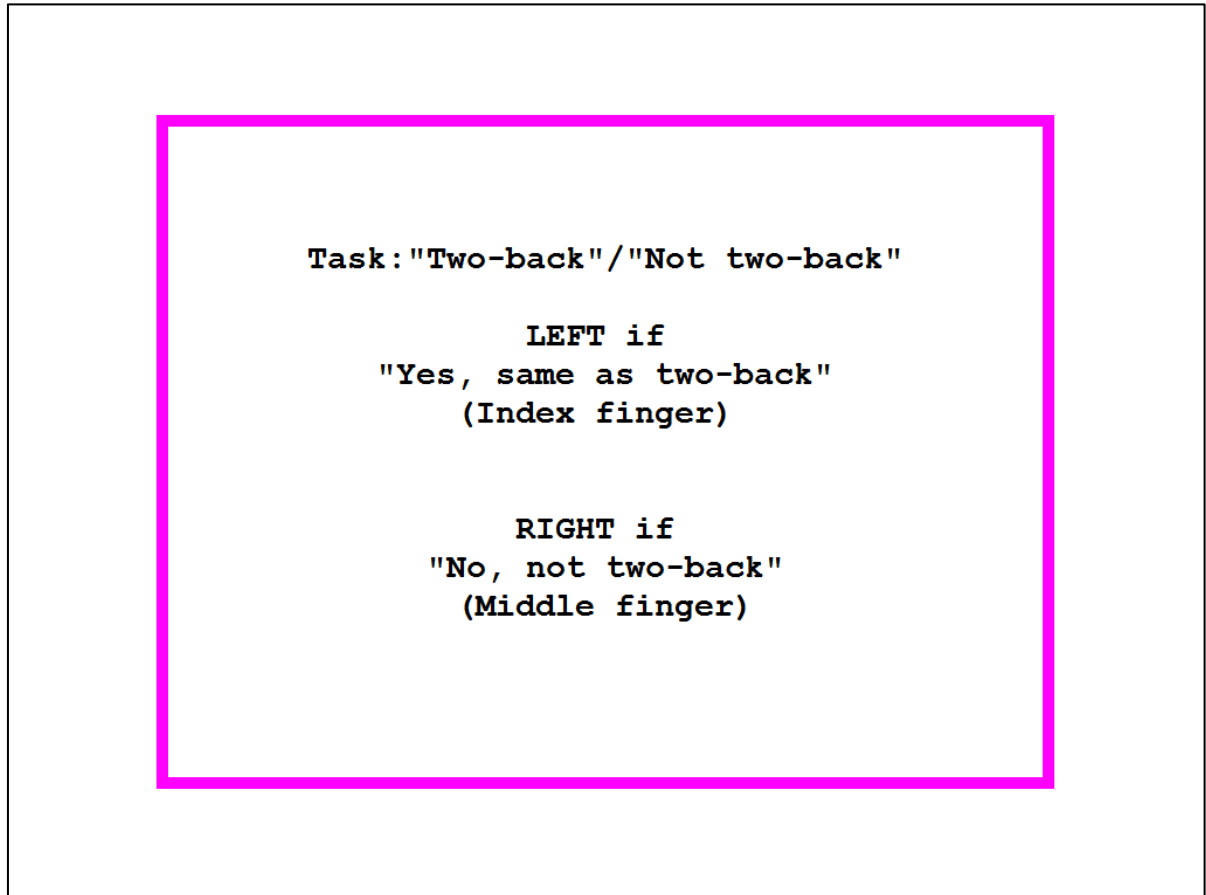


Figure 10-2. Instruction screen for the two-back task.

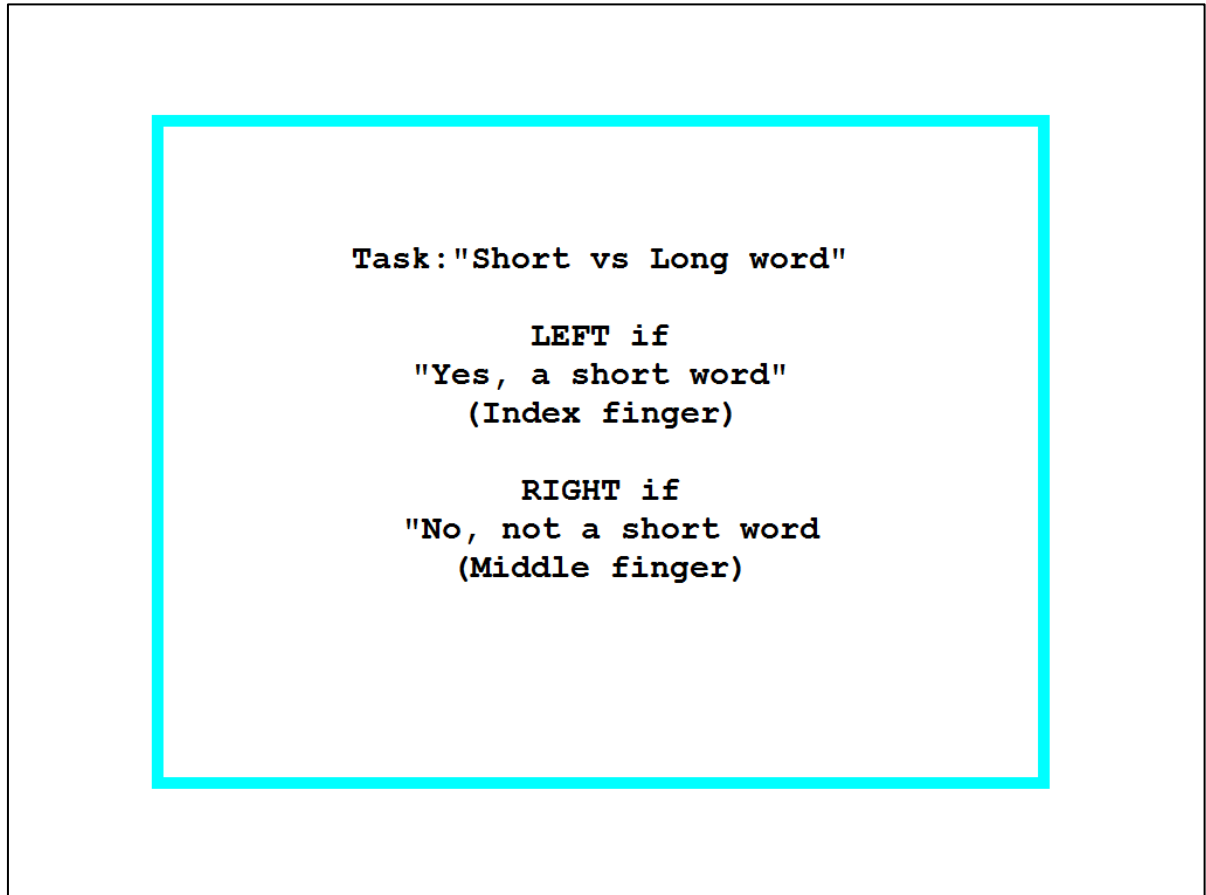


Figure 10-3. Instruction screen for the short/long task.

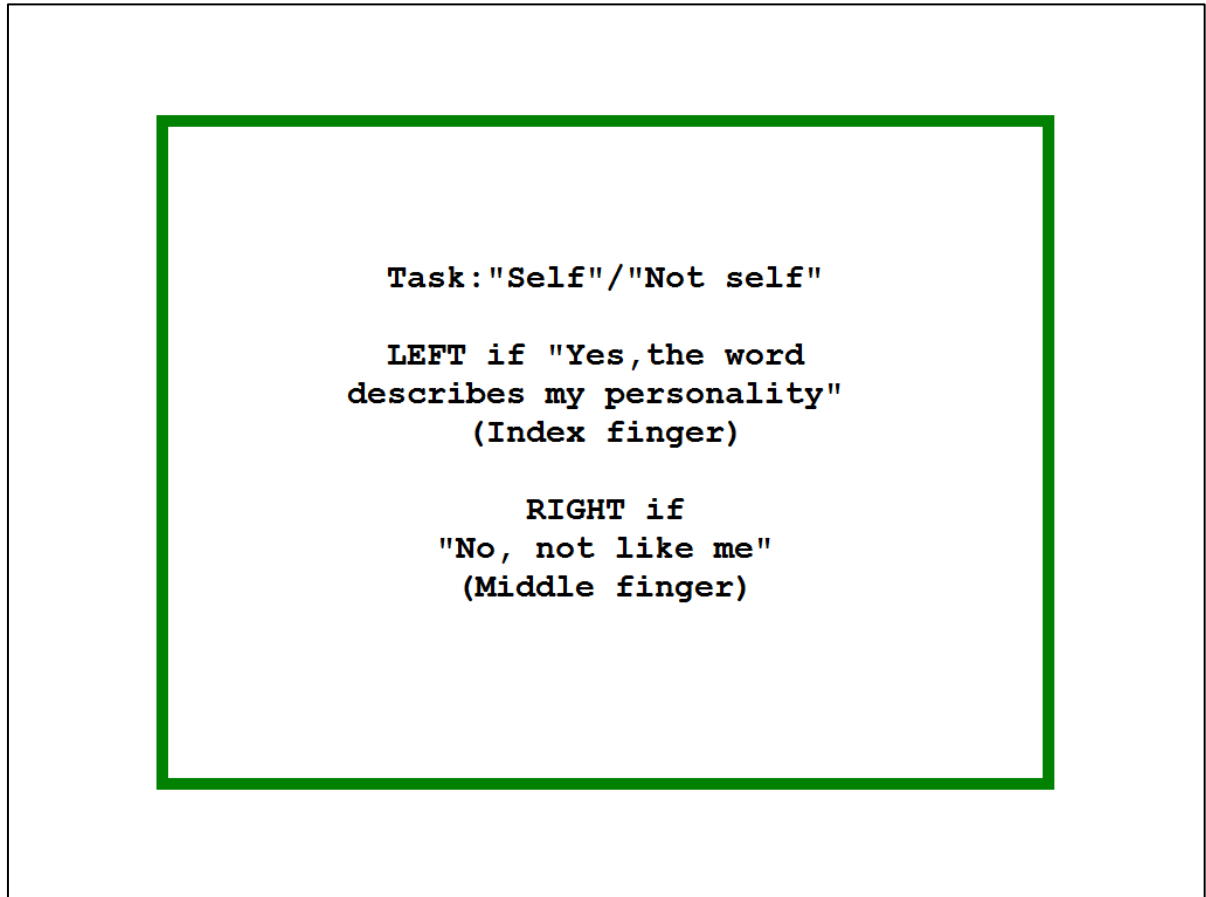


Figure 10-4. Instruction screen for the self-reflection task.